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The American Journal of Medicine

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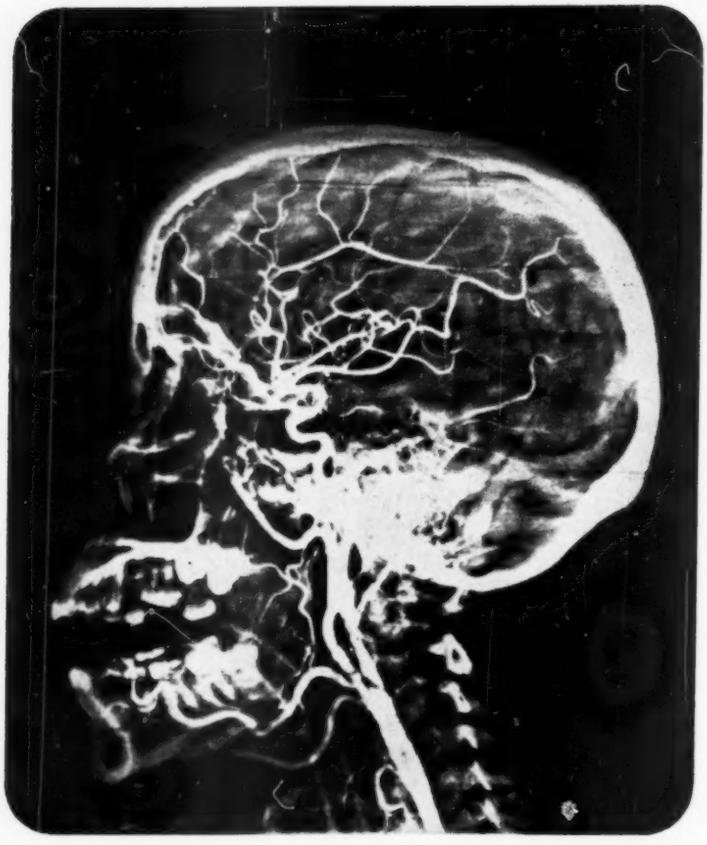

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References: (1) Doehner, G. A., and Brugger, G. E.: New York State J. Med. *60*:4022 (Dec. 15) 1960. (2) Gensini, G. G., and Ecker, A.: Radiology *75*:885 (Dec.) 1960. (3) Balkissoon, B.; Johnson, J. B.; Barber, J. B.; and Greene, C. S.: J.A.M.A. *169*:676 (Feb. 14) 1959. (4) Agnew, C. H., and Cooley, R. N.: Texas State J. Med. *55*:945 (Dec.) 1959. (5) Greenspan, R. H.; Bernstein, E. F.; and Loken, M. K.: Am. J. Roentgenol. *83*:1034 (June) 1960. (6) Kruse, C. A.: Western J. Surg. *67*:311 (Nov.-Dec.) 1959. (7) Barnett, J. C., and Arcomano, J. P.: Radiology *73*:245 (Aug.) 1959. (8) Utz, D. C., and Thompson, G. J.: Proc. Staff Meet. Mayo Clin. *33*:75 (Feb. 19) 1958. (9) Orr, L. M.; Campbell, J. L.; and Thomley, M. W.: J.A.M.A. *169*:1156 (March 14) 1959. (10) Mathews, P. W. Jr.: South. M. J. *52*:170 (Feb.) 1959.

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The authors compare the incidence of abnormally high serum triglyceride and abnormally high serum cholesterol levels in a large number of normal subjects of various ages and patients who have had myocardial infarction. Taking the figures 5.4 mEq./L. and 260 mg. per cent as the dividing lines for triglycerides and cholesterol, respectively, they find a much better correlation between abnormal serum triglyceride levels and coronary heart disease than when the serum cholesterol was used as a criterion. It is concluded, therefore, that an increase in serum triglycerides is more characteristic. The authors, wisely, do not infer that triglycerides *per se* are necessarily responsible for coronary atherosclerosis, but rather that this and other serum lipid abnormalities, such as atherosclerosis itself, are all expressions of a deeper disturbance in cellular lipid metabolism.

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KENNETH G. BERGE, RICHARD W. P. ACHOR, NORMAN A. CHRISTENSEN, HAROLD L. MASON AND NELSON W. BARKER 24

The unexpected cholesterol-lowering effect of nicotinic acid in large dosage has attracted wide attention, and this evaluation of long-term results in a sizable group of patients therefore is of interest. A statistically significant and sustained reduction in serum cholesterol was achieved, but without objective evidence of improvement in the clinical manifestations of atherosclerosis. The side reactions encountered were appreciable in number and significance, but usually not severe enough to necessitate discontinuance of therapy. The mechanism of action of nicotinic acid is obscure, but it may have to do with competition for coenzyme A between the enzyme system for biosynthesis of cholesterol and that for "detoxication" of nicotinic acid by the formation of nicotinuric acid.

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J. A. P. PARÉ, ROBERT G. FRASER, W. J. PIROZYNSKI, JOHN A. SHANKS, AND DAVID STUBINGTON 37

Fully documented, even to a genealogy dating back to 1650, this article describes a large family of which many members suffered from a genetically transferred defect in the development of the

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REFERENCES: **1.** Ellis, L. B. *et al.:* Circulation *17*:945, May 1958. **2.** Friedlander, H. S.: Am. J. Cardiol. *1*:395, Mar. 1958. **3.** Riseman, J.E.F.: New England J. Med. *261*:1017, Nov. 12, 1959. **4.** Russek, H. I. *et al.:* Circulation *12*:169, Aug. 1955. **5.** Russek, H. I.: Am. J. Cardiol. *3*:547, April 1959. **6.** Tortora, A. R.: Delaware M. J. *30*:298, Oct. 1958. **7.** Waldman, S. and Pelner, L.: Am. Pract. & Digest Treat. *8*:1075, July 1957.

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cardiac and vascular musculature hitherto included in the category of idiopathic cardiomegaly under various names, but here designated hereditary cardiovascular dysplasia. The most common symptomatology was dyspnea and syncope, with several sudden deaths, but many members had inapparent abnormalities revealed only in the electrocardiogram or roentgenogram. Autopsy in three cases disclosed hypertrophy and fibrosis of the myocardium, hypoplasia of the aorta, and an unusual localized hypertrophy of the interventricular septum (previously described in connection particularly with impingement on the aortic valve) with bizarre arrangement of the muscle fibers. The whole doubtless constitutes an entity, although variable in its manifestations, representing a developmental or metabolic anomaly.

Congenital Aortic Regurgitation. Clinical and Hemodynamic Findings in Four Patients CHARLES J. FRAHM, EUGENE BRAUNWALD AND ANDREW G. MORROW 63

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Clinicopathologic Conference

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(1) Danowski, T. S.: Diabetes Mellitus, Baltimore, Williams & Wilkins, 1957, p. 239. (2) McCune, W. G.: M. Clin. North America 44:1479, 1960. (3) Ackerman, R. F., et al.: Diabetes 7:398, 1958.

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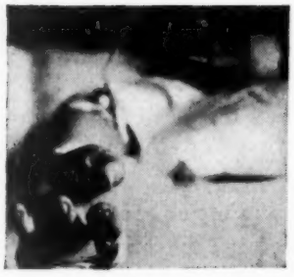

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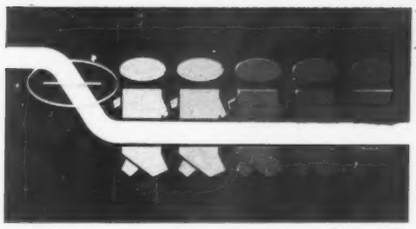

Diabinese®

BRAND OF CHLORPROPAMIDE

the oral antidiabetic most likely to succeed

economical once-a-day dosage

IN BRIEF

DIABINESE, a potent sulfonylurea, provides smooth, long-lasting control of blood sugar permitting economy and simplicity of low, once-a-day dosage. Moreover, DIABINESE often works where other agents have failed to give satisfactory control.

INDICATIONS: Uncomplicated diabetes mellitus of stable, mild or moderately severe nonketotic, maturity-onset type. Certain "brittle" patients may be helped to smoother control with reduced insulin requirements.

ADMINISTRATION AND DOSAGE: Familiarity with criteria for patient selection, continued close medical supervision, and observance by the patient of good dietary and hygienic habits are essential.

Like insulin, DIABINESE dosage must be regulated to individual patient requirements. Average maintenance dosage is 100-500 mg. daily. For most patients the recommended starting dose is 250 mg. given once daily. Geriatric patients should be started on 100-125 mg. daily. A priming dose is not necessary and should not be used; most patients should be maintained on 500 mg. or less daily. Maintenance dosage above 750 mg. should be avoided. Before initiating therapy, consult complete dosage information.

SIDE EFFECTS: In the main, side effects, e.g., hypoglycemia, gastrointestinal intolerance, and neurologic reactions, are related to dosage. They are not encountered frequently on presently recommended low dosage. There have been, however, occasional cases of jaundice and skin eruptions primarily due to drug sensitivity; other side effects which may be idiosyncratic are occasional diarrhea (sometimes sanguineous) and hematologic reactions. Since sensitivity reactions usually occur within the first six weeks of therapy, a time when the patient is under very close supervision, they may be readily detected. Should sensitivity reactions be detected, DIABINESE should be discontinued.

PRECAUTIONS AND CONTRAINDICATIONS: If hypoglycemia is encountered, the patient must be observed and treated continuously as necessary, usually 3-5 days, since DIABINESE is not significantly metabolized and is excreted slowly. DIABINESE as the sole agent is not indicated in juvenile diabetes mellitus and unstable or severely "brittle" diabetes mellitus of the adult type. Contraindicated in patients with hepatic dysfunction and in diabetes complicated by ketosis, acidosis, diabetic coma, fever, severe trauma, gangrene, Raynaud's disease, or severe impairment of renal or thyroid function. DIABINESE may prolong the activity of barbiturates. An effect like that of disulfiram has been noted when patients on DIABINESE drink alcoholic beverages.

SUPPLIED: As 100 mg. and 250 mg. scored chlorpropamide tablets.

More detailed professional information available on request.

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DONNAGEL®

Donnatal® with Kaolin and Pectin compound

Robins

DONNAGEL's comprehensive antidiarrheal formulation gives the green light to normal activity, through its fast and dependable control of intestinal hypermotility.

Each 30 cc. (1 fl. oz.) of DONNAGEL contains:

Kaolin	6.0 Gm.	Natural belladonna alkaloids:	
Pectin	142.8 mg.	hyoscyamine sulfate	0.1037 mg.
Phenobarbital (¼ gr.)	16.2 mg.	atropine sulfate	0.0194 mg.
		hyoscine hydrobromide	0.0065 mg.

also available

DONNAGEL® WITH NEOMYCIN • DONNAGEL®-PG

DONNAGEL plus neomycin sulfate 300 mg. (as neomycin base 210 mg.) per 30 cc.

DONNAGEL plus powdered opium U.S.P. 24.0 mg. per fl. oz. (equivalent to paregoric 6 ml.). This is the usual adult dose.

All three forms available in bottles of 6 fl. oz.

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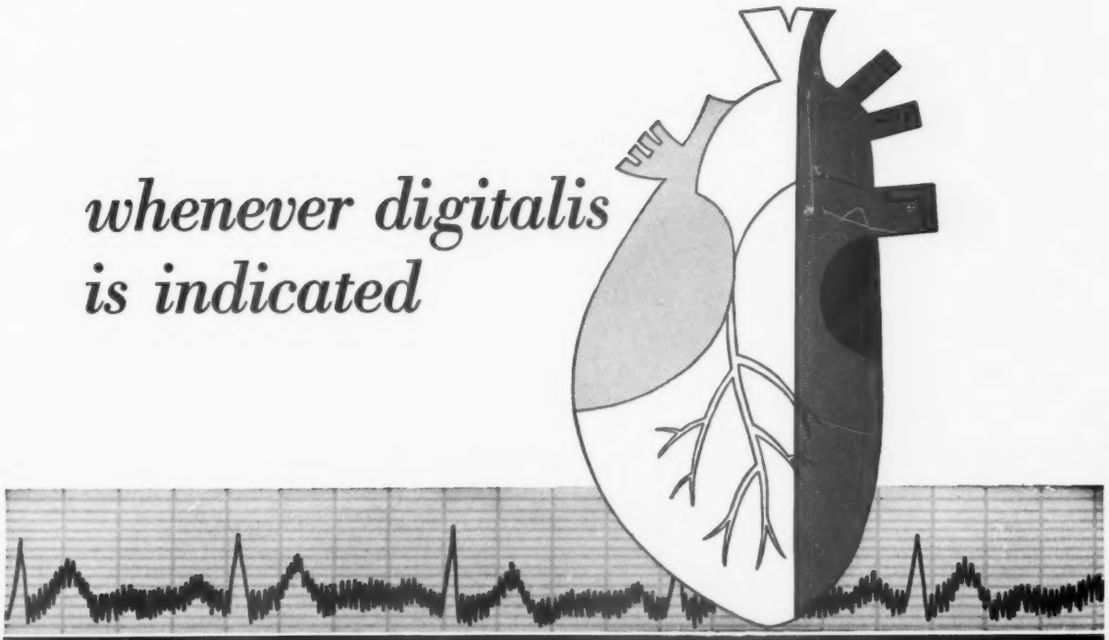
whenever digitalis is indicated



'LANOXIN'® brand DIGOXIN

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"If one digitalis agent were to be recommended for its adaptability to the many and varied clinical contingencies, we believe Digoxin would be the drug of choice."

Lown, B., and Levine, S. A.: Current Concepts in Digitalis Therapy, Boston, Little, Brown & Company, 1954, p. 23, par. 2.

'LANOXIN' TABLETS	'LANOXIN' INJECTION	'LANOXIN' ELIXIR PEDIATRIC
0.25 mg. scored (white) 0.5 mg. scored (green)	0.5 mg. in 2 cc. (I.M. or I.V.)	0.05 mg. in 1 cc.

BURROUGHS WELLCOME & CO. (U.S.A.) INC., Tuckahoe, N.Y.

Allergic or inflammatory flare-up!

Female, 41; Dx: dermatitis venenata. Contactant: calamine-antihistamine lotion applied for contact dermatitis—Rx Celestone Tablets, 0.6 mg. Photograph prior to Rx.

Step-down dosage of 1 tab. q.i.d. for 2 days, 1 tab. t.i.d. for 2 days, 1 tab. b.i.d. for 2 days and 1 tab. daily for 8 days. Results: condition completely cleared. Side Effects: none. Photograph after 72 hours of Celestone therapy. (Photographs courtesy of M. M. Nierman, M.D., Calumet City, Ill.)

Schering

Rapid remission with new Celestone

the first major advance in corticosteroid therapy in over 2½ years

Clinical worth: CELESTONE provides greatly enhanced antiallergic and anti-inflammatory effects with significantly lower mg. dosages. Its efficacy and safety have been established by 20 months of pre-introductory clinical trials in such steroid-responsive disorders as:

- bronchial asthma
- pollenosis (severe hay fever)
- allergic/inflammatory dermatoses
- inflammatory eye diseases
- rheumatoid arthritis

Exceptional utility: From simple dermatoses to the more severe steroid-responsive conditions, the unexcelled anti-inflammatory effect of CELESTONE provides rapid clinical improvement with average daily dosages of from 2 to 8 tablets.

Ease of use: CELESTONE has simple-to-follow dosage schedules for all steroid-responsive disorders based on a single tablet strength, 0.6 mg. Patients may be switched easily from other corticosteroids to CELESTONE with proper dosage adjustments.

Safety-speed factor: CELESTONE is particularly valuable for short-term therapy of acute inflammatory episodes because inflammation is resolved quickly, thus helping to avoid certain corticoid side effects such as:

- weight loss
- anorexia
- vertigo
- severe headache
- sodium and water retention
- muscle weakness
- potassium excretion

Improved response: CELESTONE also offers the advantage of providing an opportunity to restore "lost" or diminished control in patients receiving other steroids.

For complete details, consult latest Schering literature available from your Schering Representative or the Medical Services Department, Schering Corporation, Bloomfield, New Jersey.

Bibliography: 1. Goldman, L.: Investigation of a New Steroid in Dermatology. Paper presented at First Symposium on the Clinical Application of Betamethasone: A New Corticosteroid, New York City, May 8, 1961. 2. Nierman, M. M.: The Use of Betamethasone in Dermatology. *Ibid.* 3. Gant, J. Q., and Gould, A. H.: Betamethasone: A Clinical Study. *Ibid.* 4. Frank, L.: The Place of Betamethasone in Dermatologic Practice. *Ibid.* 5. Hampton, S. F.: Betamethasone—A New Steroid in Allergy: A Preliminary Report. *Ibid.* 6. Bukantz, S. C.: Observations on the Use of Betamethasone in the Intractable Asthmatic Child. *Ibid.* 7. Bedell, H.: A New Systemic Steroid in the Treatment of Allergies in Office Practice. *Ibid.* 8. Schwartz, E.: Clinical Evaluation of Betamethasone in Chronic Intractable Bronchial Asthma. *Ibid.* 9. Kammerer, W. H.: Observations on the Effects of Betamethasone in Rheumatoid Arthritis. *Ibid.* 10. Cohen, A., and Goldman, J.: Management of Rheumatoid Arthritis with a New Steroid. *Ibid.* 11. Gordon, D. M.: Betamethasone—A New Corticosteroid in Ophthalmology. *Ibid.* 12. Abrahamson, I. A., Jr.: A Clinical Evaluation of Betamethasone. *Ibid.*

H-371

(betamethasone) **Tablets, 0.6 mg.**

CELESTONE™

a new magnitude in corticosteroid activity

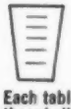
STOPS THE ASTHMA ATTACK IN MINUTES...FOR HOURS... ORALLY

ELIXOPHYLLIN®

RAPID RELIEF IN MINUTES—in 15 minutes[1,2,3] mean theophylline blood levels are comparable to I. V. aminophylline—so that severe attacks have been terminated in 10 to 30 minutes.[1,4,5,6]

SUSTAINED RELIEF FOR HOURS—After absorption theophylline is slowly eliminated during a 9-hour period,[7] making possible t.i.d. 'round-the-clock protection in chronic cases. **Note:** *With Elixophyllin the patient can learn to abort an attack in its incipient stage.*

NO UNNEEDED SIDE EFFECTS—Since Elixophyllin does not need "auxiliaries," it contains no ephedrine—no barbiturate—no iodide—no steroid. *Gastric distress is rarely encountered.*[8,9]



Each tablespoonful (15 cc.) contains theophylline 80 mg. (equivalent to 100 mg. aminophylline) in a hydro-alcoholic vehicle (alcohol 20%).

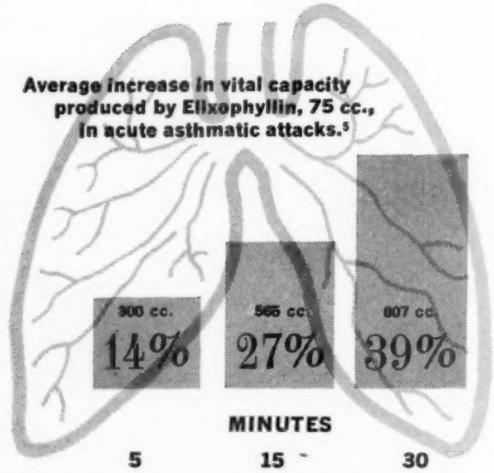
ACUTE ATTACKS:

single dose of 75 cc. for adults; 0.5 cc. per lb. of body weight for children.

24 HOUR CONTROL:

for adults 45 cc. doses before breakfast, at 3 P.M., and before retiring; after two days, 30 cc. doses. Children, first 6 doses 0.3 cc.—then 0.2 cc. per lb. of body weight as above.

Average increase in vital capacity produced by Elixophyllin, 75 cc., in acute asthmatic attacks.[5]



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Patent Pending **Reprints on request**

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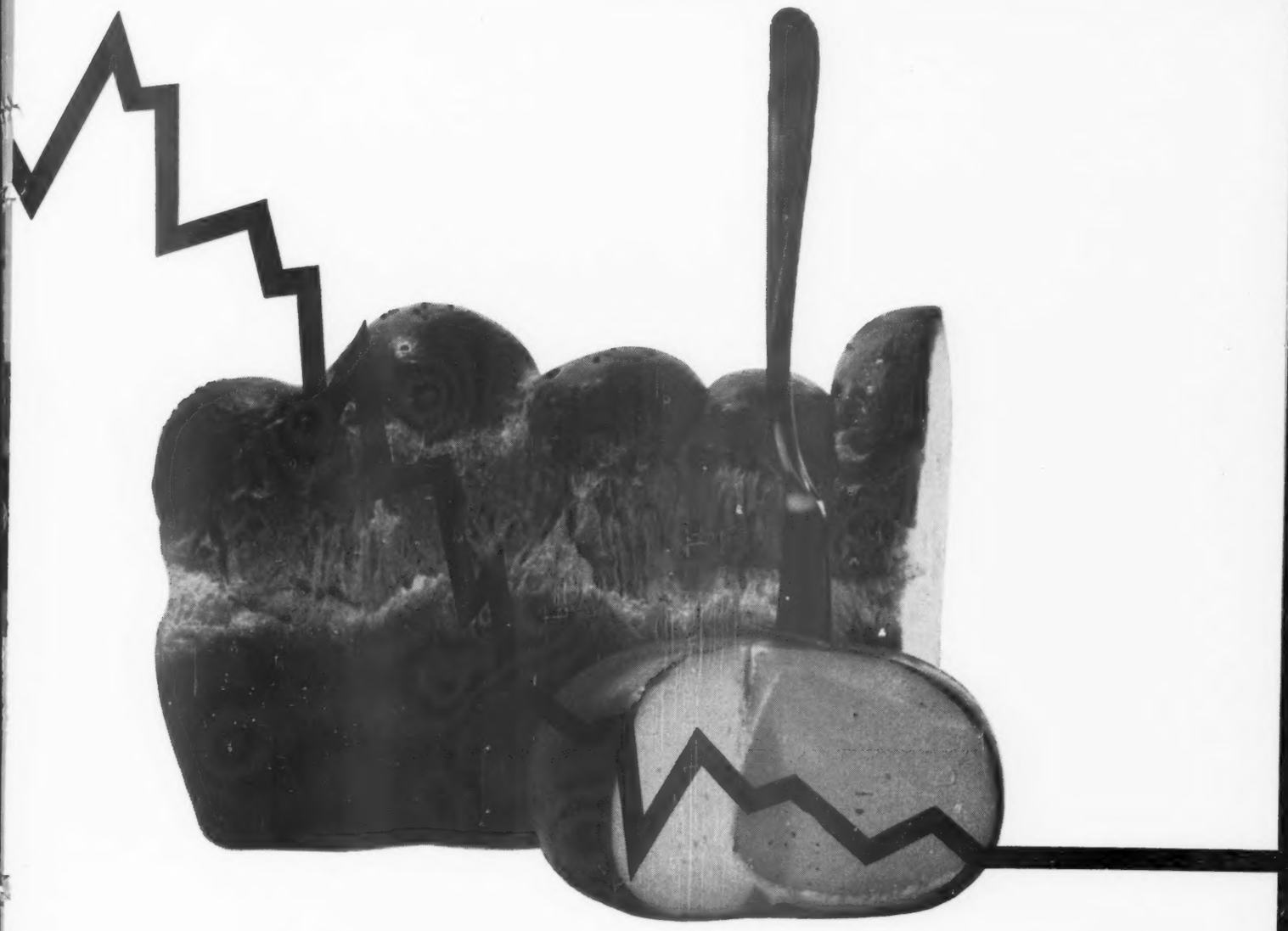

Adding Orinase may improve control significantly in diabetics now imperfectly managed on diet alone.[1-4]

Orinase releases native insulin via physiologic channels, giving the patient direct metabolic support. And Orinase dosage is flexible and readily individualized.

To improve control in many diabetics on dietotherapy — add Orinase. It can make a gratifying clinical difference.

Indications: Orinase is indicated as the therapeutic agent of choice in the majority of selected cases of adult or maturity-onset type of diabetes mellitus. In certain patients with labile diabetes, the use of Orinase as a supplement to insulin therapy may effect stabilization of the diabetic condition and lower insulin requirement.

Dosage:

Patients not receiving insulin — There is no fixed regimen for initiating Orinase therapy, but a suggested method is:

First day — 6 Orinase tablets (3.0 Gm.). **Second day** — 4 Orinase tablets (2.0 Gm.). **Third day** — 2 Orinase tablets (1.0 Gm.). **Fourth and subsequent days** — 2 Orinase tablets (1.0 Gm.) with increase or decrease as necessary to control glycosuria.

There is no fixed maintenance dose of Orinase; therapy may be individualized according to patient response. Adjust the maintenance dose (usually 1 to 4 tablets) to the smallest dose consistent with good control. The daily maintenance dose may be given once daily or in divided doses.

Patients receiving insulin (less than 20 units) — discontinue insulin and institute Orinase; (20 to 40 units) — initiate Orinase with a concurrent 30 to 50% reduction in insulin dose with a further careful reduction as response to Orinase is observed; (more than 40 units) — reduce insulin by 20% and initiate Orinase with a further careful reduction in insulin dosage as response to Orinase is observed.

Cautions: Observe all standard diabetes precautions: dietary restriction, weight control, exercise, hygiene, avoidance of infection, and adherence to dosage. As with exogenous insulin, changes in dosage may be necessary during the course of management. In the event of stress conditions, trauma or infection, increased dosage or supplementary animal insulin may be required.

Contraindications: Orinase as the sole therapeutic agent is contraindicated in juvenile diabetes; unstable or brittle diabetes; and diabetes complicated by ketosis, acidosis or coma.

Side effects: Side effects are mild, transient and limited to approximately 3% of patients. Hypoglycemia and toxic reactions are extremely rare. Hypoglycemia is most likely to occur during the period of transition from insulin to Orinase. Other untoward reactions to Orinase are usually not of a serious nature and consist principally of gastrointestinal disturbances, headache, and variable allergic skin manifestations. The gastrointestinal disturbances (nausea, epigastric fullness, heartburn) and headache appear to be related to the size of the dose, and they frequently disappear when dosage is reduced to maintenance levels or the total daily dose is administered in divided portions after meals. The allergic skin manifestations (pruritus, erythema, and urticarial, morbilliform, or maculopapular eruptions) are transient reactions, which frequently disappear with continued drug administration. However, if the skin reactions persist, Orinase should be discontinued.

Clinical toxicity: Orinase appears to be remarkably free from gross clinical toxicity on the basis of experience accumulated during more than four years of clinical use. Crystalluria or other untoward effects on renal function have not been observed. Long term studies of hepatic function in humans and experience in over 600,000 diabetics have shown Orinase to be remarkably free of hepatic toxicity. There has been reported only one case of cholestatic jaundice related to Orinase administration, which occurred in a patient with pre-existing liver disease and which rapidly reversed upon discontinuance of the drug.

Each tablet contains:

Tolbutamide ..... 0.5 Gm.

Supplied in bottles of 50.

References:

1. Bollinger, R. E., *et al.*: J. Kansas M. Soc. *61*:135 (March) 1960. 2. Williams, R. H.: Diabetes, New York, Paul B. Hoeber, Inc., 1960, pp. 491, 492. 3. Bradley, R. F.: Ann. New York Acad. Sc. *82*:513 (Sept. 25) 1959. 4. Sherry, S., *et al.*: Ann. New York Acad. Sc. *71*:249 (July 10) 1957.

Orinase*

Upjohn

An exclusive methyl "governor" minimizes hypoglycemia.

The Upjohn Company, Kalamazoo, Michigan

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* Optimum results are obtained by gradually increasing the dosage to the maximum the patient can tolerate without the appearance of drowsiness. The following procedure for dosage adjustment has proven highly successful:

Take one tablet 2 times per day for 2 days. On the third day increase the daily dosage by one tablet. Similarly increase the dose every third day thereafter, to the point of drowsiness.

For example, if one tablet 4 times a day produces an obvious sleepy feeling, and on three the patient is comfortable, then the proper dose will be three tablets per day.

a superior daytime relaxing agent

(NOT A TRANQUILIZER)

PLEXONAL®

Comparative clinical studies show that PLEXONAL is superior to meprobamate or barbiturates for daytime relaxation[1,2]

"Plexonal was preferred (superior therapeutic effect) by 73.7 per cent of the patients, whereas 11.1 per cent preferred meprobamate, a ratio of 6.6 to 1. . . . 30.5 per cent noted adverse reactions to meprobamate as compared to 7 per cent in respect to Plexonal. . . . Plexonal gave better results than did any of the sedative or relaxing agents that have been available during our experience covering the previous 15 years."[1]

In 26 older age cardiac patients, "A comparison of Plexonal with the therapy previously employed showed that 17 did better on Plexonal than on meprobamate, 6 did better on meprobamate than on Plexonal and 3 responded the same to both."[2]

Indications: Anxiety, tension, apprehension, nervousness, irritability, restlessness, hyperexcitability.

Extremely well tolerated by geriatric patients who need mild sedation, as well as by depressed patients.

Dosage: One tablet 3 or 4 times a day is adequate for most patients. However, some require up to six tablets per day, whereas others respond adequately to as little as 1 tablet per day.*

Composition: Each tablet contains sodium diethylbarbiturate 45 mg., sodium phenylethylbarbiturate 15 mg., sodium isobutylallylbarbiturate 25 mg., scopolamine hydrobromide 0.08 mg., dihydroergotamine methanesulfonate 0.16 mg.

1. Scheifley, C. H.: Proc. Staff Meet. Mayo Clin. 34:408 (Aug. 19) 1959.
2. Davanloo, H.: Am. J. of Psychiat. 117:740 (Feb.) 1961.

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Dosage: Adults — 1 tablet q.i.d. *Supplied:* 200 mg. tablets (yellow), bottles of 100. *Precautions:* Side effects have been minimal but may include CNS stimulation or, rarely, palpitation. Full dosage information, available on request, should be consulted before initiating therapy.

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for the tense and nervous patient

1 simple dosage schedule relieves anxiety dependably – without the unknown dangers of "new and different" drugs

2 does not produce ataxia, stimulate the appetite or alter sexual function

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Usual dosage: One or two 400 mg. tablets t.i.d.
Supplied: 400 mg. scored tablets, 200 mg. sugar-coated tablets; bottles of 50. Also as MEPROTABS*–400 mg. *unmarked*, coated tablets; and in *sustained-release* capsules as MEPROSPAN®-400 and MEPROSPAN®-200 (containing respectively 400 mg. and 200 mg. meprobamate).
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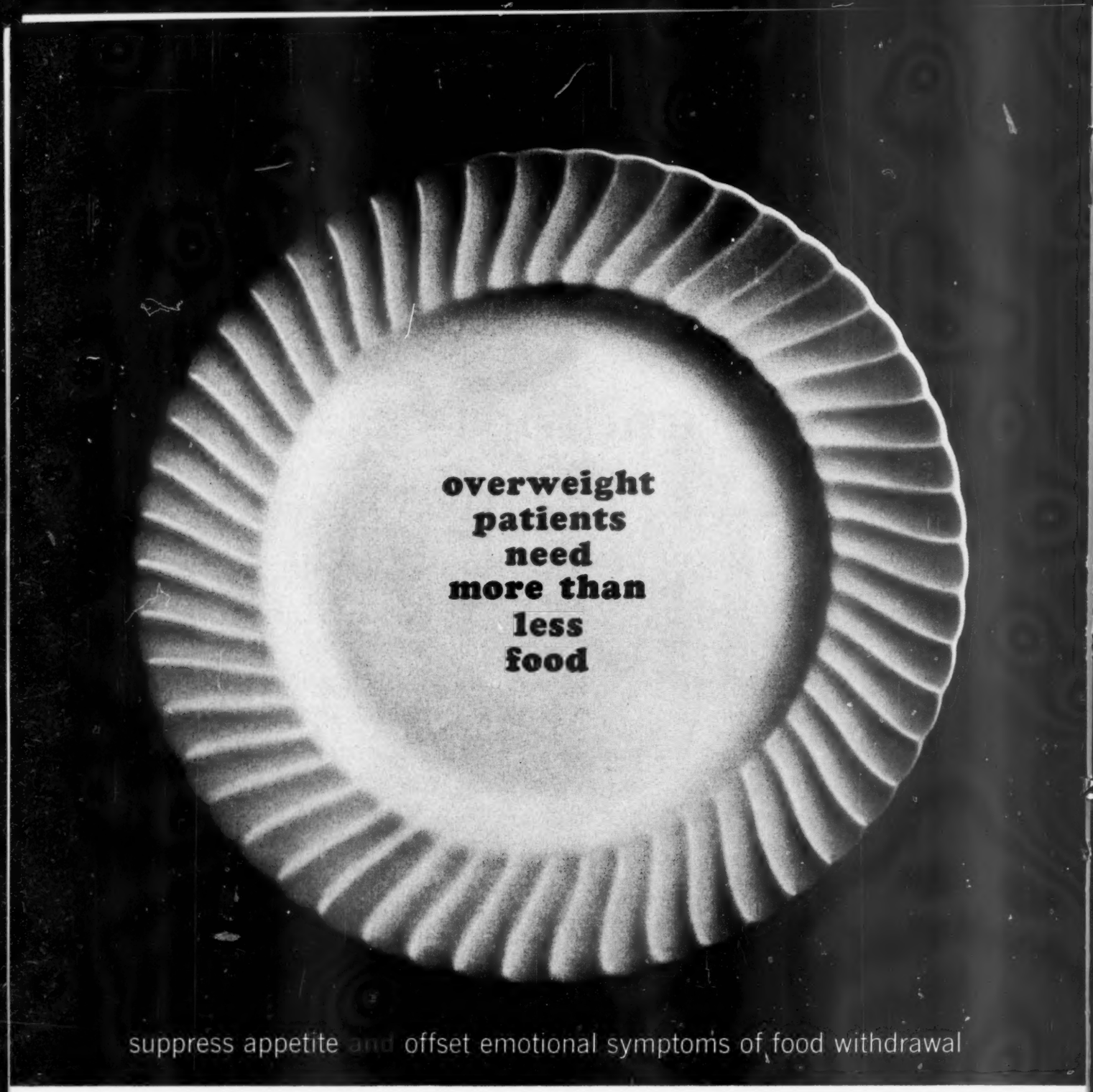

suppress appetite and offset emotional symptoms of food withdrawal

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contain an optimal ratio of methamphetamine and phenobarbital to suppress appetite **and** ease emotional symptoms of food withdrawal. The improved mental outlook produced by Ambar provides the extra encouragement the patient needs to successfully complete a balanced over-all weight-reduction plan. Ambar Extentabs are available in two methamphetamine strengths to accommodate individual patient response to sympathomimetic amines and to meet the varying requirements of the overweight and the obesity prone.

Supplied: Each **Ambar #2 Extentab** contains: Methamphetamine HCl 15 mg., phenobarbital 64.8 mg. (1 gr.). Each **Ambar #1 Extentab** contains: Methamphetamine HCl 10.0 mg., phenobarbital 64.8 mg. (1 gr.). One Extentab® before breakfast provides appetite and mood control for 10 to 12 hours, in a single, controlled-release, extended action tablet.

Also available are regular **AMBAR TABLETS.** Each contains methamphetamine HCl 3.33 mg., phenobarbital 21.6 mg., (⅓ gr.). For use in conventional dosage schedules (one or two t.i.d.), or for intermittent or supplemental therapy.

Precautions: Administer Ambar with caution to patients with cardiovascular disease or hyperthyroidism. Contraindicated in those with idiosyncrasies toward barbiturates or sympathomimetics. Occasional side effects such as nervousness or excitement have been noted, but are usually infrequent and slight when Ambar's recommended dosages are followed.

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PHARMACEUTICALS RESEARCH

5-year study[1] with COUMADIN demonstrates: long-term anticoagulation in office management of outpatients is practical and effective

A 5-year study[1] of long-term anticoagulation with COUMADIN (warfarin sodium) in office practice patients has demonstrated that such treatment reduces the probability of further infarctions in the postinfarct patient and is effective in preventing a first infarction in patients with angina.

An earlier report[2] noted that long-term anticoagulant therapy with warfarin sodium can be carried out, along with the necessary prothrombin time determinations, as part of general office practice.

"The most significant advantage is the great ease in maintaining patients in a therapeutic range. It has been rewarding to find, month after month, patients varying no more than three or four seconds in their prothrombin times on their established dosage of Warfarin sodium [COUMADIN]."[1]

COUMADIN*

FOR ORAL, INTRAVENOUS OR INTRAMUSCULAR USE

the original and only warfarin responsible for establishing this drug as closely approaching the ideal anticoagulant[3,4] and as "the best anticoagulant available today."[5] Over 179,000,000 doses administered to date.

the proven anticoagulant for long-term maintenance

Full range of oral and parenteral dosage forms—COUMADIN* (warfarin sodium) is available as: Scored tablets—2 mg., lavender; 5 mg., peach; 7½ mg., yellow; 10 mg., white; 25 mg., red. Single Injection Units—one vial, 50 mg., and one 2 cc. ampul Water for Injection; one vial, 75 mg., and one 3 cc. ampul Water for Injection.

Average Dose: Initial, 40-60 mg. For elderly and/or debilitated patients, 20-30 mg. Maintenance, 5-10 mg. daily, or as indicated by prothrombin time determinations.

1. Nora, J. J.: M. Times, May, 1961. 2. Nora, J. J.: J.A.M.A. 174:118, Sept. 10, 1960. 3. Baer, S., et al.: J.A.M.A. 167:704, June 7, 1958. 4. Meyer, K. M.: Disease-a-Month, Chicago, Yr. Bk. Pub., Mar., 1960, p. 13. 5. Meyer, O. O.: Postgrad. Med. 24:110, Aug., 1958.

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inside as well as outside the hospital... staphylococci usually remain sensitive to

CHLOROMYCETIN®

(chloramphenicol, Parke-Davis)

That the sensitivity patterns of "street" staphylococci differ widely from those of "hospital" staphylococci is a well-established clinical fact.[1-5] Although strains of staphylococci encountered in general practice have remained relatively sensitive to a number of antibiotics,[6] the problem of antibiotic-resistant staphylococci appears to be a threat to all patients in hospitals today. It is encouraging to note, however, "...that a relatively small percentage of strains develop resistance to chloramphenicol, despite the consumption of large amounts of this antibiotic."[7]

In one hospital, for example, CHLOROMYCETIN "...was the only widely used antibiotic to which few of the strains were resistant."[8] In another hospital, despite steadily increasing use of CHLOROMYCETIN since 1956, "...the percentage of chloramphenicol-resistant strains has actually been lower in subsequent years."[1] Elsewhere, insofar as hospital staphylococci are concerned, it appears that "...the problem of antibiotic resistance can be regarded as minimal for chloramphenicol."[2]

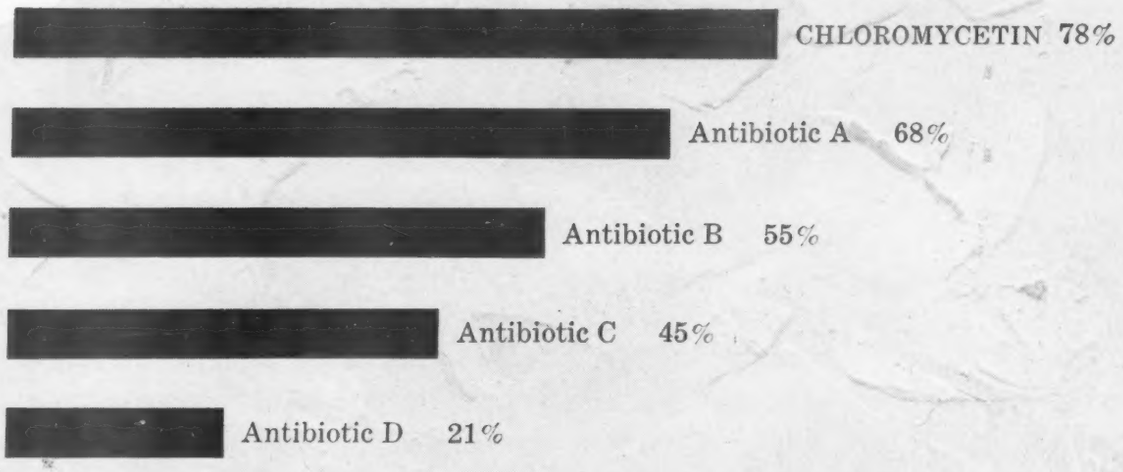
CHLOROMYCETIN (chloramphenicol, Parke-Davis) is available in various forms, including Kapseals® of 250 mg., in bottles of 16 and 100.

See package insert for details of administration and dosage.

Warning: **Serious and even fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, granulocytopenia) are known to occur after the administration of chloramphenicol. Blood dyscrasias have occurred after short-term and with prolonged therapy with this drug. Bearing in mind the possibility that such reactions may occur, chloramphenicol should be used only for serious infections caused by organisms which are susceptible to its antibacterial effects. Chloramphenicol should not be used when other less potentially dangerous agents will be effective, or in the treatment of trivial infections such as colds, influenza, viral infections of the throat, or as a prophylactic agent.**

Precautions: **It is essential that adequate blood studies be made during treatment with the drug. While blood studies may detect early peripheral blood changes such as leukopenia or granulocytopenia, before they become irreversible, such studies cannot be relied upon to detect bone marrow depression prior to development of aplastic anemia.**

IN VITRO SENSITIVITY OF 250 STRAINS OF STAPHYLOCOCCI TO CHLOROMYCETIN AND TO FOUR OTHER ANTIBIOTICS*



These strains of coagulase-positive staphylococci were isolated from hospitalized patients at a large county hospital during the year 1959. Sensitivity tests were done by the disc method.

*Adapted from Bauer, Perry, & Kirby[1]

References: (1) Bauer, A. W.; Perry, D. M., & Kirby, W. M. M.: *J.A.M.A.* 173:475, 1960. (2) Fisher, M. W.: *Arch. Int. Med.* 105:413, 1960. (3) Cohen, S.: *Circulation* 20:96, 1959. (4) Edwards, T. S.: *Am. J. Ophth.* 48, Part II:19, 1959. (5) Smith, I. M.: Staphylococcal Infections, Chicago, The Year Book Publishers, Inc., 1958, p. 148. (6) Petersdorf, R. G.; Rose, M. C.; Minchew, H. B.; Keene, W. R., & Bennett, I. L., Jr.: *Arch. Int. Med.* 105:398, 1960. (7) Editorial: *J.A.M.A.* 173:544, 1960. (8) Finland, M.; Jones, W. F., Jr., & Bennett, I. L., Jr.: *Arch. Int. Med.* 104:365, 1959.

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(Dihydromorphinone HCl)

swift, sure analgesia normally unmarred by nausea and vomiting

DILAUDID provides unexcelled analgesia in acute cardiovascular conditions. Onset of relief from pain is almost immediate. The high therapeutic ratio of DILAUDID is commonly reflected by lack of nausea and vomiting—and marked freedom from other side-effects such as dizziness and somnolence.

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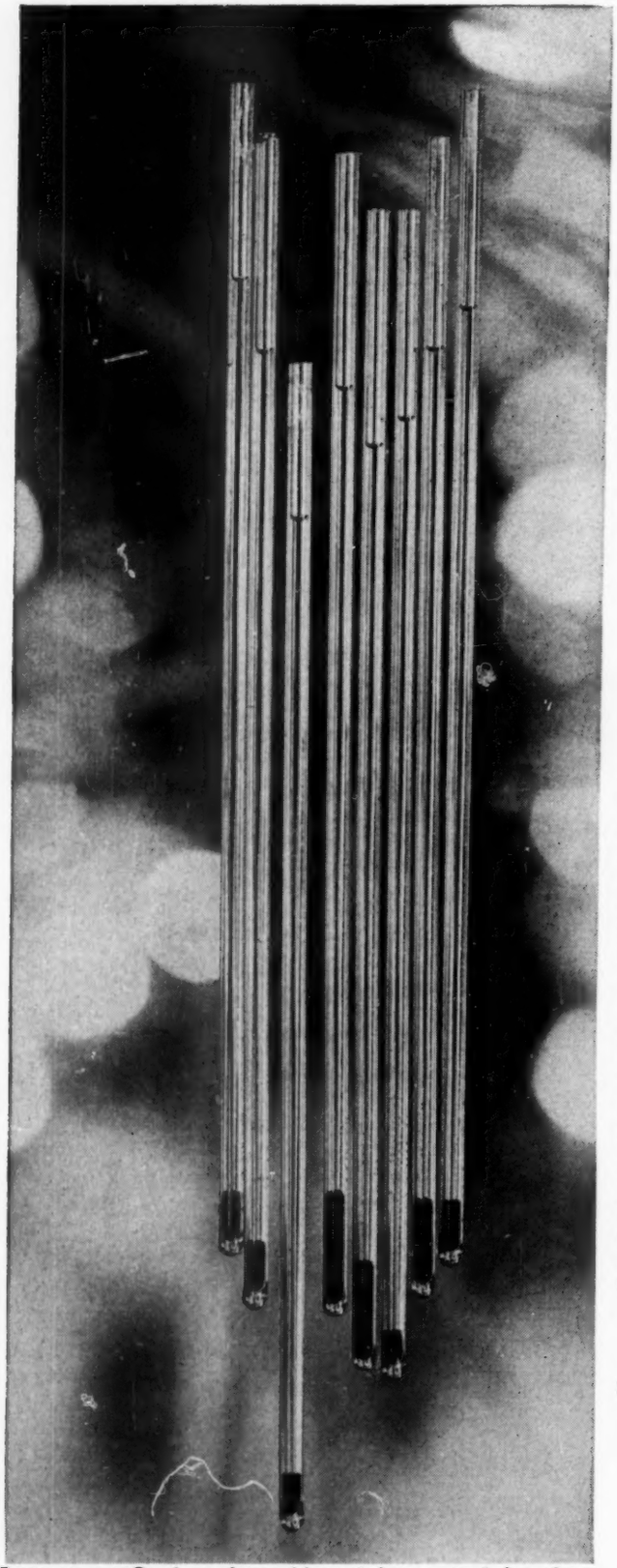

IMMUNOCRIT® tubes, pictured here 4 times actual size, show results of centrifuging patients' serums with BETA-L TEST antiserum. Longest columns of precipitate indicate high beta-lipoprotein levels.

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The growing evidence implicating beta-lipoprotein as one of the agents responsible for atherosclerosis has emphasized the need for a test procedure which is reliable, yet simple enough to be suited to clinical purposes.[1] Hyland BETA-L TEST answers this need. BETA-L TEST results show a close correlation with complex quantitative methods now in use, yet BETA-L TEST can be performed in ten minutes on one drop of serum and employs a minimum of laboratory equipment and technical skill.[2]

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1. Wood, F. C., Gurin, S., and Kuo, P. T.: Medical Correlation Clinic on Atherosclerosis and Coronary Artery Disease, Am. Pract.–Dig. Treat. *12:* 235 (April) 1961.

2. Heiskell, C. L., Fisk, R. T., Florsheim, W. H., Yachi, A., Goodman, J. R., and Carpenter, C. M.: A Simple Method for Quantitation of Serum Beta-Lipoproteins by Means of the Immunocrit, Amer. J. Clin. Path. *35:* 222 (March) 1961.

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Reference: 1. Bunim, J. J., in Hollander, J. L.: Arthritis and Allied Conditions, ed. 6, Philadelphia, Lea & Febiger, 1960, p. 364.

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TREATS MORE PATIENTS MORE EFFECTIVELY

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broad antibacterial range
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OPHTHOCORT provides:

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References: (1) Morrison, W. H.: *Nebraska M. J.* 45:106, 1960. (2) Perkins, E. S.: *Practitioner* 178:575, 1957. (3) Tassman, W. S.: *U. S. Armed Forces M. J.* 10:161, 1959. (4) Kamiya, S.: *Am. J. Ophth.* 42:269, 1956. (5) Holland, R. W. B.: *Arch. Ophth.* 57:214, 1957. (6) Benton, C. D., Jr.: *South M. J.* 51:1562, 1958. (7) Blakiston's New Gould Medical Dictionary, ed. 2, New York, McGraw-Hill Book Company, Inc., 1956, p. 945. (8) Ostler, H. B., & Braley, A. E.: *J. Iowa M. Soc.* 44:427, 1954.

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Relief of Anxiety and Tachycardia...
Bradycrotic and Gentle Tranquilizing Action

DOSAGE: One or two tablets q.i.d. before meals and h.s.

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in prepartum tension and anxiety		allays anxiety without impairing ability to cooperate during labor and delivery[1]	reduces narcotic requirements and incidence of narcotic-induced respiratory depression, helps control emesis[1,4]
in the cardiac or the hypertensive patient		allays anxiety without adverse influence on blood pressure[2]	helps correct certain functional arrhythmias, does not increase gastric secretion[2]
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in preoperative tension and anxiety		allays anxiety without depression of vital functions[4]	reduces incidence of narcotic-induced respiratory depression and hypotension, relaxes skeletal muscle, smooths recovery and helps control emesis[4]
in pediatrics		allays tension in agitated, hyperkinetic patients	avoids danger of liver damage or other untoward reactions

References: 1. Benson, C., and Benson, R. C.: Scientific Exhibit, Illinois Acad. Gen Practice, Sept., 1960. **2.** Salmons, J. A.: Dis. Chest 38:105, 1960. **3.** Major, R. A.: GP 21.104, 1960. **4.** Grady, R. W., and Rich, A. L.: Scientific Exhibit, Am. Soc. Anesth., New York, Oct. 4-7, 1960.

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IN BRIEF

Vistaril is hydroxyzine pamoate. The hydrochloride salt of hydroxyzine is used in the parenteral solution.

Vistaril acts rapidly in the symptomatic treatment of a variety of neuroses and other emotional disturbances manifested by anxiety, apprehension or fear—whether occurring alone or complicating a physical illness. Used preoperatively and prepartum, Vistaril controls anxiety and fear, permits a substantial reduction in the amount of meperidine or other narcotic required for satisfactory analgesia, and helps prevent emesis. Vistaril's calming effect usually does not impair discrimination, and is accompanied by direct and secondary muscle relaxation. No toxicity has been reported with Vistaril, and it has a remarkable record of freedom from reactions.

INDICATIONS: Vistaril is clinically effective in anxiety and tension states, senility, anxiety associated with various disease states, alcoholism, pre- and postpartum and pre- and postoperative tension and emesis, certain functional arrhythmias, and pediatric behavior problems.

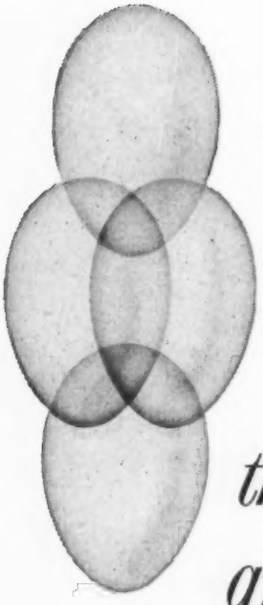
ADMINISTRATION AND DOSAGE: Dosage varies with the state and response of each patient, rather than with weight and should be individualized by the physician for optimum results. *Recommended oral dosage:* In anxiety and tension states, senility, alcoholism, pre- and postoperative and pre- and postpartum tension and emesis: up to 400 mg. daily in divided doses. In anxiety associated with asthma, neurodermatoses, menopausal syndrome, digestive disorders, functional or essential hypertension, tension headaches: 50 mg. q.i.d. initially—adjust according to response. In cardiac arrhythmias: initial—25 mg. q. 6 h. until arrhythmia disappears; maintenance or prophylactic—50-75 mg. daily in divided doses. In pediatric behavior problems under 6 years: 50 mg. daily in divided doses. Six and over: 50-100 mg. daily in divided doses. *Recommended parenteral dosage:* In preoperative, obstetrical, and more emergent situations in other indications: 25-100 mg. I.M. or I.V. q. 4 h., p.r.n. In cardiac arrhythmias: 50-100 mg. I.M. stat, and q. 4-6 h., p.r.n.; maintain with 25 mg. b.i.d. or t.i.d.

SIDE EFFECTS: Drowsiness may occur in some patients; if so, it is usually transitory, disappearing within a few days of continued therapy or upon reduction of dosage. Dryness of mouth may be encountered at higher doses.

PRECAUTIONS: The potentiating action of hydroxyzine should be taken into account when the drug is used in conjunction with central nervous system depressants. Do not exceed 1 cc. per minute I.V. Do not give over 100 mg. per dose I.V. Parenteral therapy is usually for 24-48 hours, except when, in the judgement of the physician, longer-term therapy by this route is desirable.

SUPPLIED: VISTARIL *Capsules* (hydroxyzine pamoate)—25, 50, and 100 mg. VISTARIL *Oral Suspension* (hydroxyzine pamoate)—25 mg. per 5 cc. teaspoonful. VISTARIL *Parenteral Solution* (hydroxyzine hydrochloride)—10 cc. vials, 25 mg. per cc.; 2 cc. ampules, 50 mg. per cc.

More detailed professional information available on request.



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From the infant's first introduction to semisolid food and throughout the entire growth period, the exceptional nutrient value of eggs contributes significantly to body needs.

Egg yolk is often given as the first solid food; it is part of the earliest mixed diet and is a good source of iron for infants. The typical diet prescribed at one year of age includes an egg as an important daily constituent; adequate nutrition throughout the growing years calls for the nutrients found in eggs. Why?

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One Egg Provides:*

Protein	6.5 Gm.
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Fats (total lipids)	6.0 Gm.
Fatty acids	
Saturated (total)	2.0 Gm.
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Oleic acid	2.5 Gm.
Linoleic acid	0.5 Gm.

Vitamins present: A, D, E, K, B_1, B_2, B_6, B_{12}, pantothenic acid, niacin, folic acid, biotin.

Minerals present: Calcium, phosphorus, sodium, potassium, chlorine, sulfur, iron, iodine, manganese, magnesium, zinc, copper.

**U. S. Department of Agriculture Home and Garden Bulletin No. 72, Sept. 1960.*

The nutritional statements made in this advertisement have been reviewed by the Council on Foods and Nutrition of the American Medical Association and found consistent with current authoritative medical opinion.

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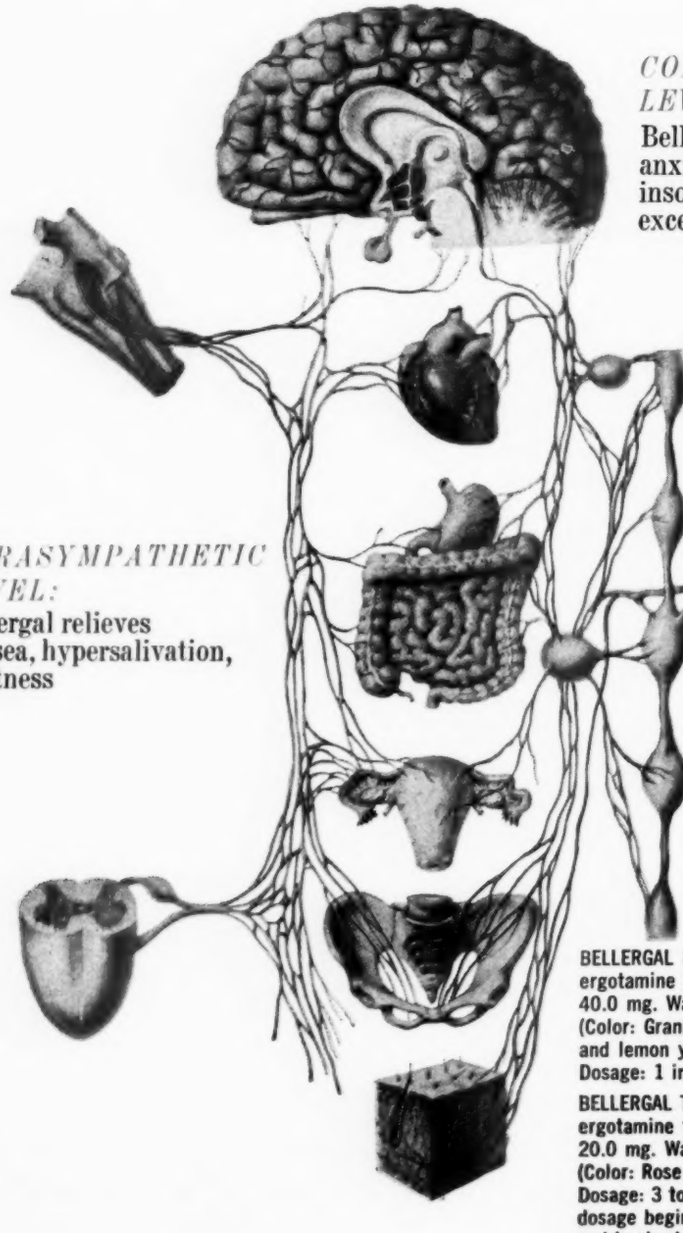

CORTICAL LEVEL:
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BELLERGAL SPACETABS—Bellafoline 0.2 mg., ergotamine tartrate 0.6 mg., phenobarbital 40.0 mg. Warning: May be habit forming. (Color: Granular pattern of green, apricot and lemon yellow; compressed.) Dosage: 1 in the morning, and 1 in the evening.

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Bibliography: 1. Kestler, O. C.: *J.A.M.A.* *171*:2039 (April 30) 1960.

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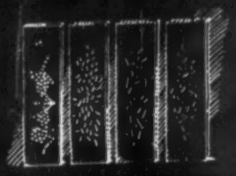

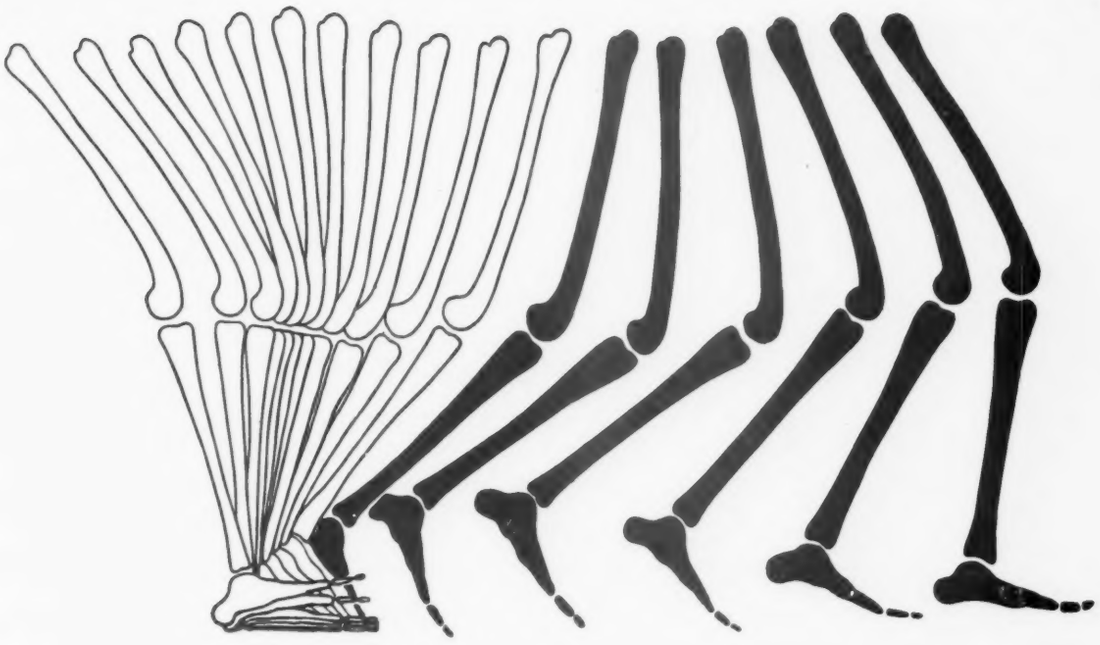

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Indications and dosages

Intra-articular, intrabursal and intratendinous injections of Depo-Medrol are useful for sustained anti-inflammatory effect and symptomatic relief in rheumatoid arthritis, osteoarthritis, bursitis, tendinitis, epicondylitis and other rheumatic disorders.

Intra-articular dosage depends on the size of the joint and the severity of the condition. Injections may be repeated, if necessary, at intervals of one to five weeks. A suggested dosage guide: Large joint, 20 to 80 mg.; medium joint, 10 to 40 mg.; small joint, 4 to 10 mg.

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Precautions

Depo-Medrol for local effect is contraindicated in the presence of acute infectious conditions. Infrequently, atrophic changes in the dermis may form shallow depressions in the skin at the injection site, but these usually disappear in a few months.

Depo-Medrol 40 mg. per cc.
Each cc. contains:

Medrol (methylprednisolone) acetate	40 mg.
Polyethylene glycol 4000	29 mg.
Sodium chloride	8.7 mg.
Myristyl-gamma-picolinium chloride	0.19 mg.
Water for injection	q.s.

Supplied: 1 cc. and 5 cc. vials

20 mg. per cc.
Each cc. contains:

Medrol (methylprednisolone) acetate	20 mg.
Polyethylene glycol 4000	29.6 mg.
Sodium chloride	8.9 mg.
Myristyl-gamma-picolinium chloride	0.19 mg.
Water for injection	q.s.

Supplied: 5 cc. vials

1. Norcross, B. M., and Winter, J. A.: Methylprednisolone acetate: a single preparation suitable for both intra-articular and systemic use, New York J. Med. *61*:552 (Feb. 15) 1961.

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1. Blank, P., and Boas, H.: Improved analgesia for moderate pain, Ann. West. Med. & Surg. 6:376, 1952. 2. Bonica, J. J., et al.: The management of postpartum pain with dihydrohydroxycodeinone (Percodan): Evaluation with codeine and placebo, West. J. Surg. 65:84, 1957. 3. Cass, L. J., and Frederick, W. S.: A controlled study in pain relief, M. Times 84:1318, 1956. 4. Chasko, W. J.: Pain-free dental surgery: Postoperative extension of the pain-free state, J. District of Columbia Dent. Soc. 31:3, No. 5, 1956. 5. Cozen, L.: Office Orthopedics, ed. 2, Philadelphia, Lea & Febiger, 1953, pp. 120, 138, 145, 156, 234. 6. Nicolson, W. P., Jr., and Skandalakis, Jr E.: Control of postoperative pain, J.M.A. Georgia 46:471, 1957. 7. Piper, C. E., and Nicklas, F. W.: Percodan for pain in industrial practice, Indust. Med. 23:510, 1954; abstracted, Clin. Med. 3:1008, 1956, Current M. Digest 22:135, No. 3, 1955.

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Indications: To supplement other sources of vitamins, minerals, hormones, digestive enzymes, and amino acids.

Dosage: One Kapseal three times daily before meals. Female patients should follow each 21-day course with a 7-day rest interval.

Precaution: Contraindicated in patients wherein estrogen or androgen therapy should not be used, as in carcinoma of the breast, genital tract, or prostate, and in patients with a familial tendency to these types of malignancy; give cautiously to females who tend to develop excessive hair growth or other signs of masculinization.

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Soma relieves stiffness –stops pain, too

YOUR CONCERN: Rapid relief from pain for your patient. Get him back to his normal activity, fast!

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YOUR RESULTS: With pain relieved, stiffness gone, your patient is soon restored to full activity—often in days instead of weeks.

Kestler reports in controlled study: *Average time for restoring patients to full activity: with Soma, 11.5 days; without Soma, 41 days. (J.A.M.A. Vol. 172, No. 18, April 30, 1960.)*

Soma is notably safe. Side effects are rare. Drowsiness may occur, but usually only in higher dosages. Soma is available in 350 mg. tablets. USUAL DOSAGE: 1 TABLET Q.I.D.

The muscle relaxant with an independent pain-relieving action

SOMA®

(carisoprodol, Wallace)

®Wallace Laboratories, Cranbury, New Jersey

Dept. S-11, Professional Services Dept.
Wallace Laboratories, Cranbury, N. J.

Gentlemen: *Please send me a physician's sample of Soma.*

Dr._____

Street_____

City_____ Zone___ State_____

Type of practice_____

I know
it is
effective

The continuing clinical effectiveness of Terramycin therapy derives as always from its proven antibiotic characteristics—rapid absorption; notably wide distribution in body tissues and fluids; high, active urinary concentrations; and a broad anti-infective spectrum embracing even such a troublesome organism as Pseudomonas. Additionally, Terramycin therapy provides the assurance of a 10-year record of exceptional toleration.

Cosa-Terramycin®

OXYTETRACYCLINE WITH GLUCOSAMINE

today's oral *form of Terramycin*

IN BRIEF

Cosa-Terramycin provides oxytetracycline (Terramycin®) with glucosamine for maximum absorption.

INDICATIONS: Because oxytetracycline is effective against both gram-positive and gram-negative bacteria, rickettsiae, spirochetes, large viruses, and certain parasites (amebae, pinworms), Cosa-Terramycin is indicated in a great variety of infections due to susceptible organisms, e.g., infections of the respiratory, gastrointestinal, and genitourinary tracts, surgical and soft-tissue infections, ophthalmic and otic infections, and many others.

ADMINISTRATION AND DOSAGE: Adults: 1 Gm. of oxytetracycline daily in four divided doses is usually effective. In *severe* infections, a larger dosage (2-4 Gm. daily) may be indicated. Infants and children: 10-20 mg. of oxytetracycline per lb. of body weight daily. Certain diseases are treated in courses.

SIDE EFFECTS AND PRECAUTIONS: Antibiotics may allow overgrowth of nonsusceptible organisms—particularly monilia and resistant staphylococci. If this occurs, discontinue medication and institute indicated supportive therapy and treatment with other appropriate antibiotics. Aluminum hydroxide gel has been shown to decrease antibiotic absorption and is therefore contraindicated. Glossitis and allergic reactions are rare. There are no known contraindications to glucosamine.

SUPPLIED: *Cosa-Terramycin Capsules,* 250 mg. and 125 mg. Terramycin is also available in: *Cosa-Terrabon® Oral Suspension,* a palatable preconstituted aqueous suspension containing 125 mg. per 5 cc. teaspoonful, bottles of 2 oz. and 1 pint; *Cosa-Terrabon® Pediatric Drops,* a palatable preconstituted aqueous suspension containing 5 mg. per drop (100 mg. per cc.), bottle of 10 cc. with calibrated plastic dropper; and *Terramycin Intramuscular Solution, conveniently preconstituted,* in the new 10 cc. multi-dose vial, 50 mg. per cc., and in 2 cc. prescored glass ampules, containing 100 mg. or 250 mg., packages of 5 and 100. In addition, a variety of other systemic and local dosage forms are available to meet specific therapeutic requirements.

More detailed professional information available on request.

Science for the world's well-being® Pfizer PFIZER LABORATORIES *Division, Chas. Pfizer & Co., Inc. Brooklyn 6, New York*

urge your patients to drink

orange juice

A rich natural source of potassium is important to you and your patients because potassium deficiency has become a serious, recurrent problem in the modern-day treatment of many diseases.

Several valuable new drugs unfortunately drain the body of potassium. Patients receiving these preparations run the danger of a potassium deficiency severe enough to disturb renal function and cause or aggravate edema. Supplementary potassium, therefore, preferably from a rich natural source like Florida orange juice, should always accompany vigorous, prolonged treatment with therapeutic agents of this type.

What better way is there to supply this necessary potassium than for your patient to drink a glass of orange juice each time he takes his medication? . . . What pleasanter source of potassium than delicious, refreshing *Florida orange juice* — either freshly squeezed, frozen, or canned? In any form orange juice is rich in potassium and vitamin C. For the heart failure patient it's important, too, that supplementary potassium tends to reduce the intensity of sodium retention and lessens the threat of edema.

Every 8-ounce glass of Florida orange juice, whether from concentrate or from fresh oranges, contains approximately 446 mg. potassium.

FLORIDA CITRUS COMMISSION, LAKELAND, FLORIDA

Three of these women have vaginitis (trichomonal, monilial or mixed). Only comprehensive therapy can reach all three.

For every 2 cases of vaginitis caused by Trichomonas vaginalis alone, there is usually 1 case caused by Candida (Monilia) albicans, Haemophilus vaginalis, or mixed infection involving several pathogens.[1-3]

You can reach all of these vaginitis patients with the *comprehensive* vaginal preparation effective against C. albicans, H. vaginalis and other bacterial pathogens, *in addition to* T. vaginalis.

1. POWDER *for weekly application in your office:* FUROXONE® (furazolidone) 0.1% and MICOFUR® (nifuroxime) 0.5%, in an acidic water-dispersible base. 15 Gm. plastic squeeze bottle. 2. SUPPOSITORIES *for continued home use:* first week 1 in the morning and 1 on retiring. After first week, 1 at night may suffice. Continue treatment during menses and throughout menstrual cycle and for several days thereafter. Contain MICOFUR 0.375% and FUROXONE 0.25% in a water-miscible base. Boxes of 12 or 24 suppositories with applicator.

TRICOFURON®

Improved

1. Coolidge, C. W.; Glisson, C. S., Jr., and Smith, A. A.: J. M. A. Georgia 48:167 (Apr.) 1959. 2. Ensey, J. E.: Am. J. Obst. & Gynec. 77:155 (Jan.) 1959. 3. Frech, H. C., and Lanier, L. R., Jr.: J. M. A. Georgia 47:498 (Oct.) 1958.

EATON LABORATORIES
Division of The Norwich Pharmacal Company
NORWICH, NEW YORK

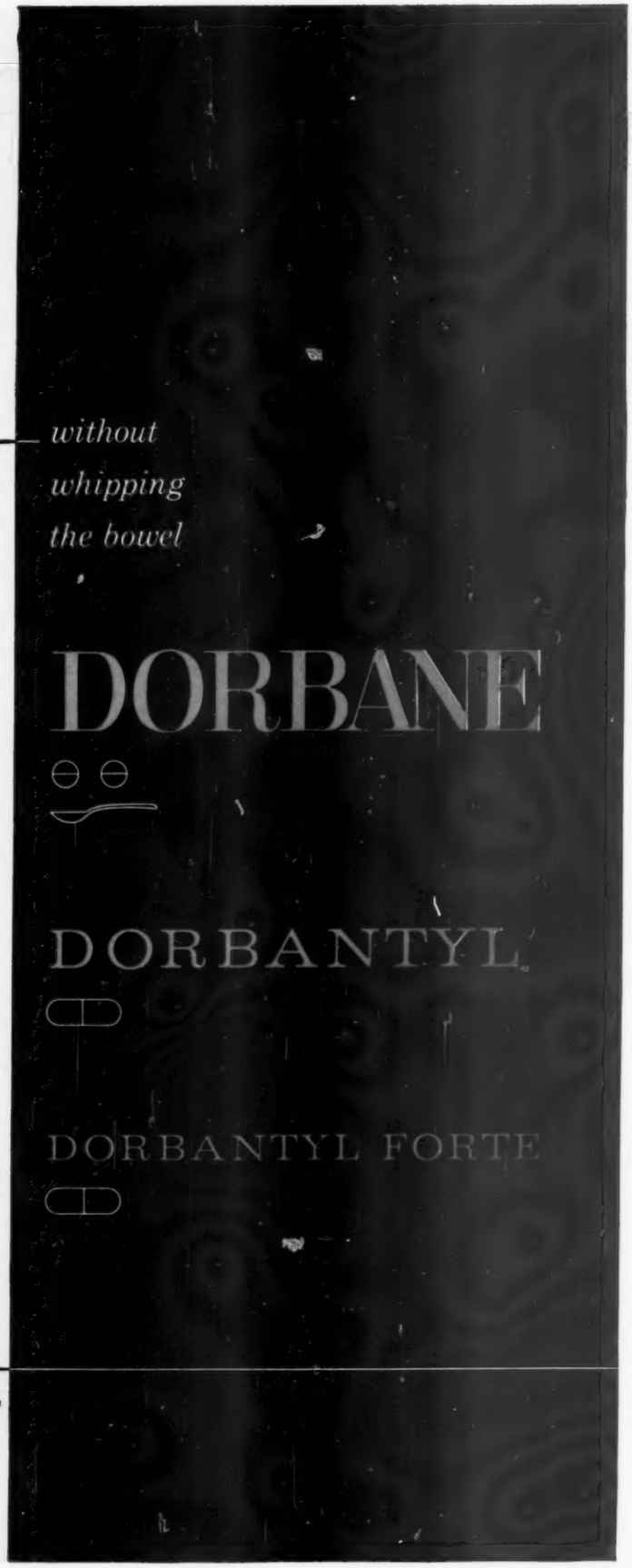
GENTLE STIMULATION OF COLONIC PERISTALSIS

without whipping the bowel

The active principle of Dorbane reaches the colon through the circulation. It acts directly and selectively upon the intrinsic plexus of the colon. The small bowel is not affected. Within 6 to 12 hours evacuation occurs without cramping or griping. Nonhabituating. Each scored tablet of Dorbane contains 75 mg., and each teaspoonful of orange-flavored liquid contains 37.5 mg. of 1,8 dihydroxyanthraquinone. Suitable for patients of all ages.

Dorbantyl combines the colonic stimulant action of Dorbane (25 mg.) with the stool-softening effect of dioctyl sodium sulfosuccinate (50 mg.), an inert and safe surface-wetting agent, in each orange-and-black capsule.

Dorbantyl Forte offers double strength dosage of the Dorbantyl combination for greater convenience and economy for patients requiring extra potency. In orange-and-gray capsules.



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Northridge, California

reducing the problems of reducing

Preludin®

brand of phenmetrazine HCl

Tablets and Endurets®
prolonged-action tablets

**an oxazine...
not an amphetamine**

Unsurpassed Effectiveness
In all controlled clinical studies, Preludin has produced impressively greater weight loss than placebo tablets regardless of the degree of enforcement of dietary restriction.

Exceptionally High Tolerance
Reports are numerous of successful use of Preludin in cases intolerant of other anorexiants.

Flexibility of Dosage
Available as scored tablets of 25 mg. for b.i.d. or t.i.d. administration and also as Endurets®, 75 mg., for once daily administration.

Precautions and Contraindications

Although there have been no reports of significant toxic reactions to Preludin, on theoretical grounds it should not be given to patients with severe hypertension, thyrotoxicosis or acute coronary disease.

Preludin may be used with caution in cases of moderate hypertension and cardiac decompensation.

Preludin®, brand of phenmetrazine hydrochloride. Under license from C. H. Boehringer Sohn, Ingelheim.

Geigy Pharmaceuticals
Division of Geigy Chemical Corporation
Ardsley, New York

Geigy

PR 877-61

the first complete physiologic regulator of female cyclic function

ENOVID®

(BRAND OF NORETHYNODREL WITH ETHYNYLESTRADIOL 3-METHYL ETHER)

The basic action

ENOVID closely mimics the balanced progestational-estrogenic action of the functioning corpus luteum. This action is readily understood by a simple comparison. In effect, ENOVID *induces a physiologic state which simulates early pregnancy—except that there is no placenta or fetus.* Thus, as in pregnancy, the production or release of pituitary gonadotropin is inhibited and ovulation suspended; a pseudodecidual endometrium ("pseudo" because neither placenta nor fetus is present) is induced and maintained. Further, during ENOVID therapy, certain symptoms typical of normal pregnancy may be noted in some patients, such as nausea—which is usually mild and disappears spontaneously within a few days—breast engorgement, some degree of fluid retention, and often a marked sense of well-being. There is no androgenicity. ENOVID *is as safe as the normal state of pregnancy.*

The basic applications

1. Correction of menstrual dysfunction. *Cyclic* therapy with ENOVID controls dysfunctional uterine bleeding (menorrhagia, metrorrhagia) and often establishes a normal menstrual cycle in amenorrhea.

2. Ovulation suppression (to suspend fertility). For this purpose ENOVID is administered *cyclically*, beginning on day 5 through day 24 (20 daily doses). The ovary remains in a state of physiologic rest and there is no impairment of subsequent fertility. Continuous administration for more than two years is not recommended.

3. Postponement of the menses for reasons of health (impending hospitalization for surgery, during treatment of Bartholin's gland cysts, acute urethritis, rectal abscess, trichomonal or monilial vaginitis), travel, forthcoming marriage, or pressing business or professional engagements. For this purpose ENOVID may be started at any time in the cycle up to one week before expected menstruation. Upon discontinuation, normal cyclic bleeding occurs in three to five days.

4. Threatened abortion. *Continuous* ENOVID treatment provides balanced hormonal support for the endometrium in threatened or habitual abortion.

5. Endocrine infertility. ENOVID has been used successfully in *cyclic* therapy of endocrine infertility, promoting subsequent pregnancy through a probable "rebound" phenomenon.

6. Endometriosis. *Continuous* therapy with ENOVID corrects endometriosis by producing a pseudodecidual reaction with subsequent absorption of aberrant endometrial tissue.

The basic dosage

Basic dosage of ENOVID is 5 mg. daily in *cyclic* therapy, beginning on day 5 through day 24 (20 daily doses). Higher doses may be used with complete safety to prevent or control occasional "spotting" or breakthrough bleeding during ENOVID therapy, or for rapid effect in emergency treatment of dysfunctional bleeding and threatened abortion. ENOVID is available in tablets of 5 mg. and 10 mg. Literature and references, covering over five years of intensive clinical study, available on request.

SEARLE *Research in the Service of Medicine*

...unfettered

From the beginning, woman has been a vassal to the temporal demands—and frequently the aberrations—of the cyclic mechanism of her reproductive system. Now, to a degree heretofore unknown, she is permitted normalization, enhancement, or suspension of cyclic function and procreative potential. This new physiologic control is symbolized in an illustration borrowed from ancient Greek mythology—Andromeda freed from her chains.

Patient M. J. ... one of the thousands of hypertensive patients now being controlled by Ismelin®

Mr. M.J., now 61, was admitted to a large teaching hospital in 1957 with mild pulmonary edema and severe hypertension (300/170 mm. Hg). Digitalis was given, along with reserpine and a ganglionic blocker.* He was discharged 16 days later, with blood pressure of 130/70 mm. Hg standing and 170/110 supine. Blood pressure, within 4 weeks, was 170/105 mm. Hg (sitting and standing). But ganglion-blocker therapy (alone or combined with chlorothiazide and/or rauwolfia) failed to hold blood pressure down and the side effects —syncope, lightheadedness, difficulty in evacuation and micturition— became increasingly troublesome.

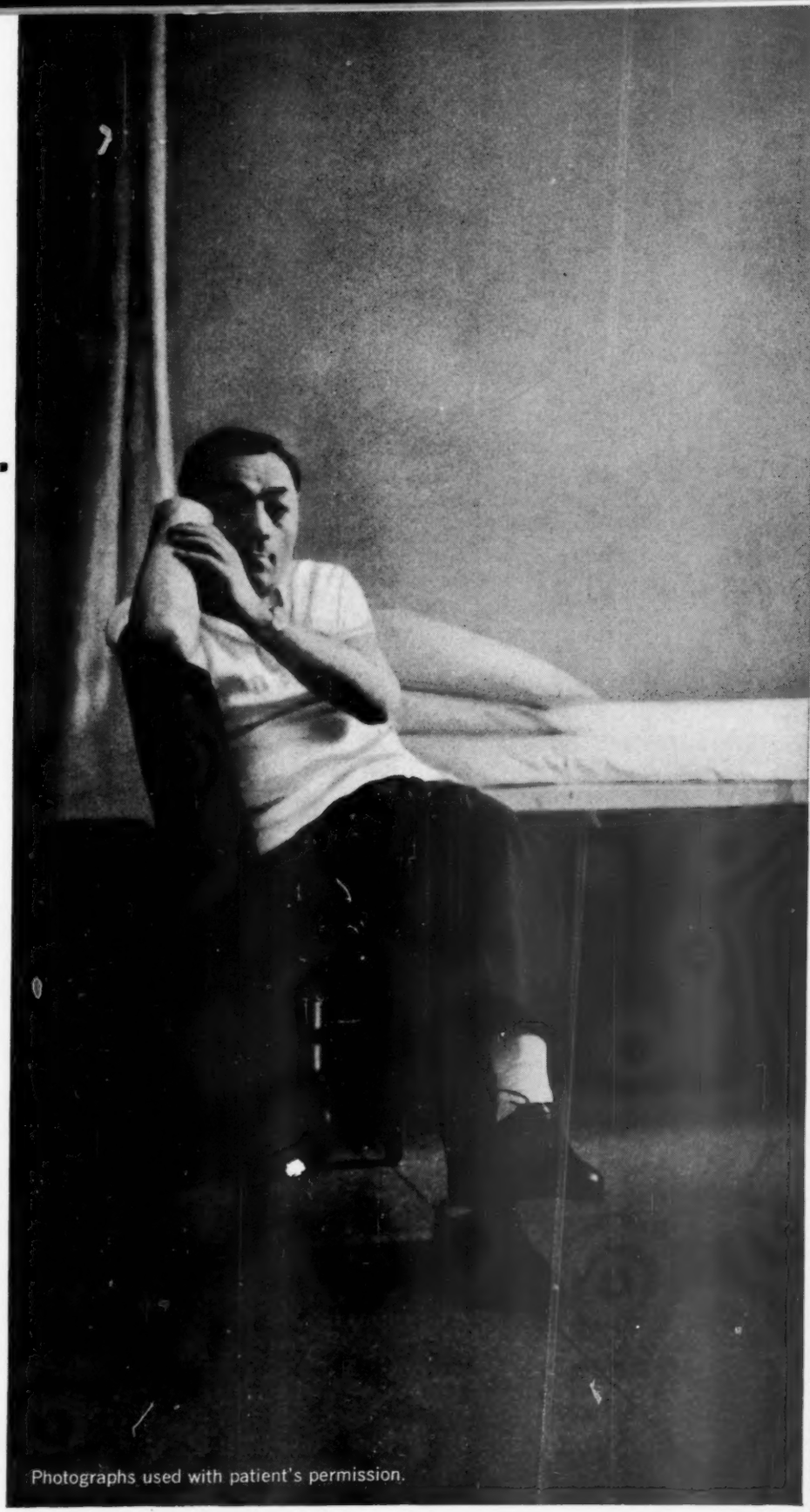
Blood pressure controlled with Ismelin— patient active and comfortable

On March 1, 1960, the ganglionic blocker was replaced with SU-5864 (Ismelin†). Within 5 weeks, Mr. J. was nearly normotensive and "felt 100% better."

As of October 5, 1960, blood pressure was 174/100 sitting and 130/80 standing. There was no evidence of tolerance to Ismelin.

*Therapy for this patient, during the 3½ years of treatment described here, included digitalis and one or more of the following: rauwolfia, thiazides, Serpasil-Apresoline.
†SU-5864 was introduced by CIBA as Ismelin® on July 5, 1960.

CIBA
SUMMIT·NEW JERSEY



Photographs used with patient's permission.

..."the most important new drug for the treatment of hypertension..."[1]

Following are representative comments from the ever-increasing published reports on Ismelin:

Patients on Ismelin have controlled blood pressures

"Only 1 of the 27 patients did not respond to treatment....The reduction of the systolic and diastolic pressures averaged 11/13 per cent in the supine position, 17/17 per cent in the sitting position, and 25/22 in the erect position. There were, of course, varying responses in the blood pressure from patient to patient, but generally blood pressure reduction was consistent in all three positions. The postural effect was most striking."[2]

"...Guanethidine [Ismelin] is a potent agent which lowers the diastolic pressure in many cases previously resistant to therapy with rauwolfia, hydralazine, hydrochlorothiazide, and ganglionic blockade."[3]

"Though our experience is limited, we have little doubt that guanethidine [Ismelin] is at present the drug of choice [for severe hypertension]. Its action is apparently steady; tolerance does not develop; and outpatient care of cases is relatively easy."[4]

"The use of this extremely potent drug led in all cases, which were treated both in hospital and on an ambulatory basis, to a clear-cut reduction in blood pressure, often even to normal levels."[5]

Hypertensive patients on Ismelin are relatively comfortable

Ismelin, because it is the selective sympathetic inhibitor, allows patients to be relatively comfortable. Ismelin suppresses sympathetic function with virtually no effect on the parasympathetic nervous system.

"In contrast [to the ganglionic blocking agents], guanethidine [Ismelin] is a purely sympatholytic agent with a hypotensive potency similar to that of the ganglion blocking compounds but with a lesser incidence of accompanying untoward effects."[6]

"The absence of tachycardia distinguishes the action of guanethidine [Ismelin] from that of adrenergic blocking drugs..."[2]

"Guanethidine [Ismelin], administered alone, was given to 40 hypertensive patients without serious side effects."[7]

"Notably absent were the constipation, paresis of visual accommodation, and dry mouth characteristic of the parasympatholytic effects of ganglion blocking drugs."[8]

"The absence of constipation was especially noteworthy."[9]

"Diarrhea has been mild and easily controlled."[10]

"Dry mouth, constipation, and difficulty in micturition were not encountered in this study. Those patients who had previously been on ganglion blocking therapy were relieved of these symptoms remarkably quickly, as well as of blurring of vision, when [Ismelin] was substituted."[11]

"No serious side effects were seen, and all could be alleviated or abolished by reducing the dosage."[7]

Physicians note that patients prefer Ismelin

"The majority of patients preferred guanethidine [Ismelin] over their previous antihypertensive medications; those previously treated with ganglionic blocking agents were particularly grateful for relief of constipation and visual difficulties."[7]

"We believe that use of it lessened anxiety in our patients. Most were better satisfied with guanethidine than they had been with previous ganglion blocker therapy."[11]

"Unlike the impotence experienced after ganglionic blocking agents, ability to obtain an erection was not impaired."[2]

"Guanethidine [Ismelin] has remarkably few side effects. The absence of symptoms of parasympathetic blockade makes its use better tolerated by most patients than conventional ganglion blocking therapy."[11]

"Most patients who had been treated previously with ganglion-blocking drugs expressed a strong preference for guanethidine."[12]

"Life need no longer be made a misery by the parasympathetic effects of the ganglion-blocking agents."[4]

For complete information about Ismelin (including dosage, cautions, and side effects), see 1961 Physicians' Desk Reference or write CIBA, Summit, N. J.

SUPPLIED: Tablets, 10 mg. (pale yellow, scored) and 25 mg. (white, scored); bottles of 100.

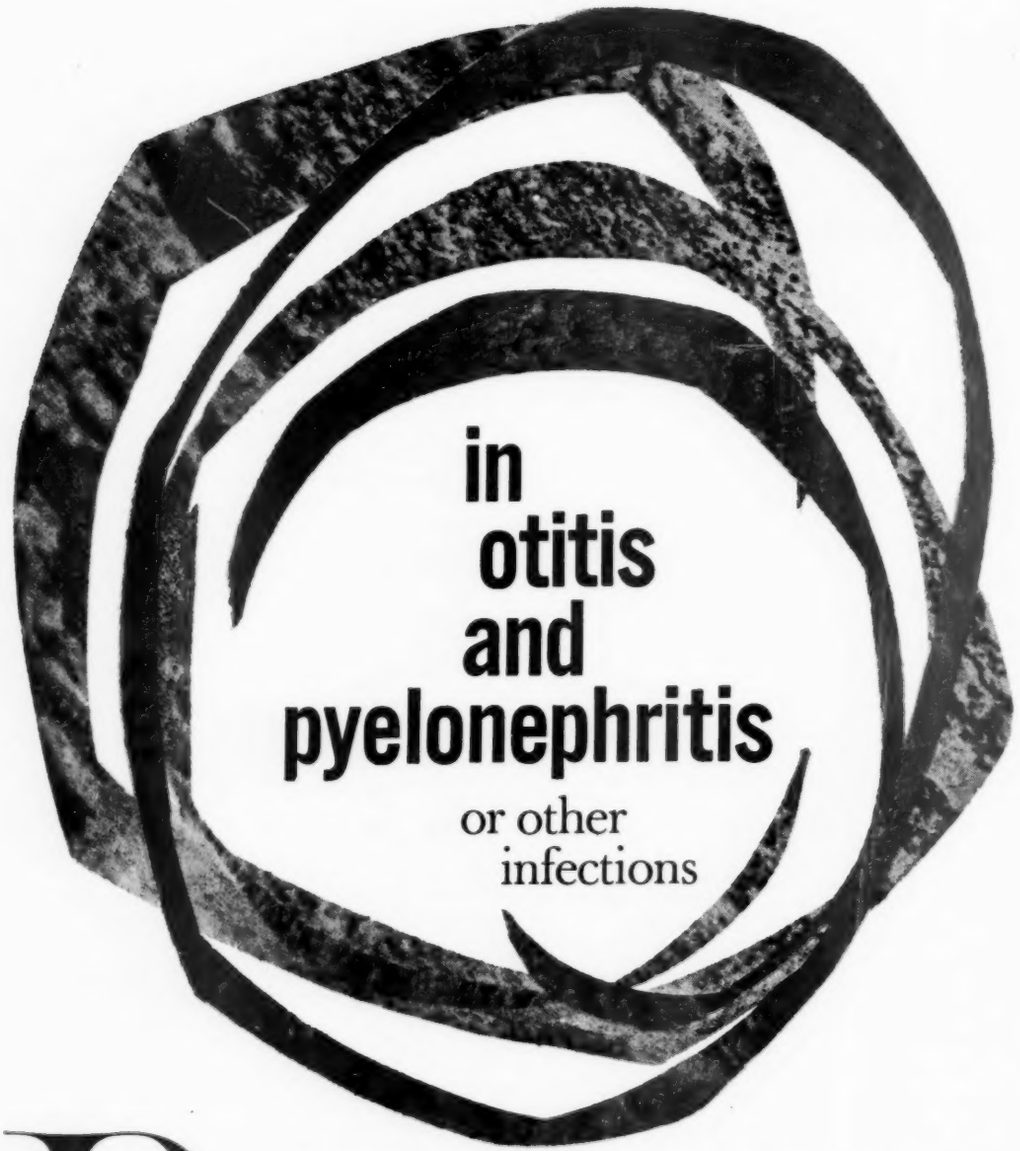
REFERENCES: 1. Kirkendall, W. M., Freis, E. D., and Moyer, J. H.: Summary of panel discussion, "New Drugs in the Treatment of Hypertension," presented at the 33rd Scientific Sessions of the American Heart Association, St. Louis, Mo., Oct. 21, 1960. 2. Frohlich, E. D., and Freis, E. D.: Paper presented at a Symposium on Guanethidine (Ismelin®), The University of Tennessee College of Medicine, Memphis, Tenn., April 22, 1960. 3. Clark, G. M., Edmonson, J., and Lefkovits, A.: Ibid. 4. Evanson, J. M., and Sears, H. T. N.: Lancet 2:387 (Aug. 20) 1960. 5. Jaquerod, R., and Spühler, O.: Schweiz. med. Wchnschr. 90:113 (Jan. 30) 1960 (translation). 6. Brest, A. N., and Moyer, J. H.: Paper presented at a Symposium of Guanethidine (Ismelin®), The University of Tennessee College of Medicine, Memphis, Tenn., April 22, 1960. 7. Eagan, J. T., and Orgain, E. S.: Ibid. 8. Richardson, D. W., and Wyso, E. M.: Virginia M. Month. 86:377 (July) 1959. 9. Ford, R. V., and Fallis, N.: Paper presented at a Symposium on Guanethidine (Ismelin®), The University of Tennessee College of Medicine, Memphis, Tenn., April 22, 1960. 10. Page, I. H., and Dustan, H. P.: J.A.M.A. 170:1265 (July 11) 1959. 11. Kirkendall, W. M., Fitz, A. M., Van Hecke, D. C., Wilson, W. R., and Armstrong, M. L.: Ibid. 12. Dollery, C. T., Emslie-Smith, D., and Milne, M. D.: Lancet 2:381 (Aug. 20) 1960.

2/2964MB

SERPASIL®-APRESOLINE® hydrochloride
(reserpine and hydralazine hydrochloride CIBA)
ESIDRIX® (hydrochlorothiazide CIBA)

Ismelin®

sulfate
(guanethidine sulfate CIBA)



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DECLOMYCIN®

DEMETHYLCHLORTETRACYCLINE LEDERLE

against relapse—up to 6 days' activity on 4 days' dosage
against secondary infection—sustained high activity levels
against "problem" pathogens—positive broad-spectrum antibiosis

CAPSULES, 150 mg., 75 mg.; PEDIATRIC DROPS, 60 mg./cc.; SYRUP, 75 mg./5 cc.

Request complete information on indications, dosage, precautions and contraindications from your Lederle representative or write to Medical Advisory Department.

LEDERLE LABORATORIES, A Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

Rheumatoid arthritis

Use of oral Medrol:

In severe or moderately severe cases, initial dosage of Medrol tablets is 8 to 16 mg. daily; maintenance dosage ranges from 4 to 12 mg. daily, adjusted stepwise every 5 to 10 days in accordance with response. In children, and also in adults with moderate disease, both initial and maintenance dosage is Medrol 4 to 8 mg. daily.

"It [methylprednisolone] is potent and displays a slightly improved 'safety' record, showing a reduced frequency of disturbing side-effects as compared with the other steroids."

—Neustadt, D. H.: J.A.M.A. *170*:1253 (July 11) 1959.

Medrol*

Upjohn

75th year

Indications and effects

Medrol benefits (anti-inflammatory, antiallergic, antirheumatic, antileukemic, antihemolytic) have been demonstrated in acute rheumatic carditis, rheumatoid arthritis, asthma, hay fever and allergic disorders, dermatoses, blood dyscrasias, and ocular inflammatory disease involving the posterior segment.

Precautions and contraindications

Because of Medrol's high therapeutic ratio, patients usually experience dramatic relief *without* developing such possible steroid side effects as gastrointestinal intolerance, weight gain or weight loss, edema, hypertension, acne, or emotional imbalance.

As in all corticotherapy, however, there are certain cautions to be observed. The presence of diabetes, osteoporosis, chronic psychotic reactions, predisposition to thrombophlebitis, hypertension, congestive heart failure, renal insufficiency, or active tuberculosis necessitates careful control in the use of steroids. Like all corticosteroids, Medrol is contraindicated in patients with arrested tuberculosis, peptic ulcer, acute psychoses, Cushing's syndrome, herpes simplex keratitis, vaccinia, or varicella.

Each tablet contains: Medrol (methylprednisolone) . . . . . 2, 4, or 16 mg.
Medrol is supplied as 2 mg. tablets in bottles of 30 and 100; as 4 mg. tablets in bottles of 30, 100 and 500; and as 16 mg. tablets in bottles of 50.

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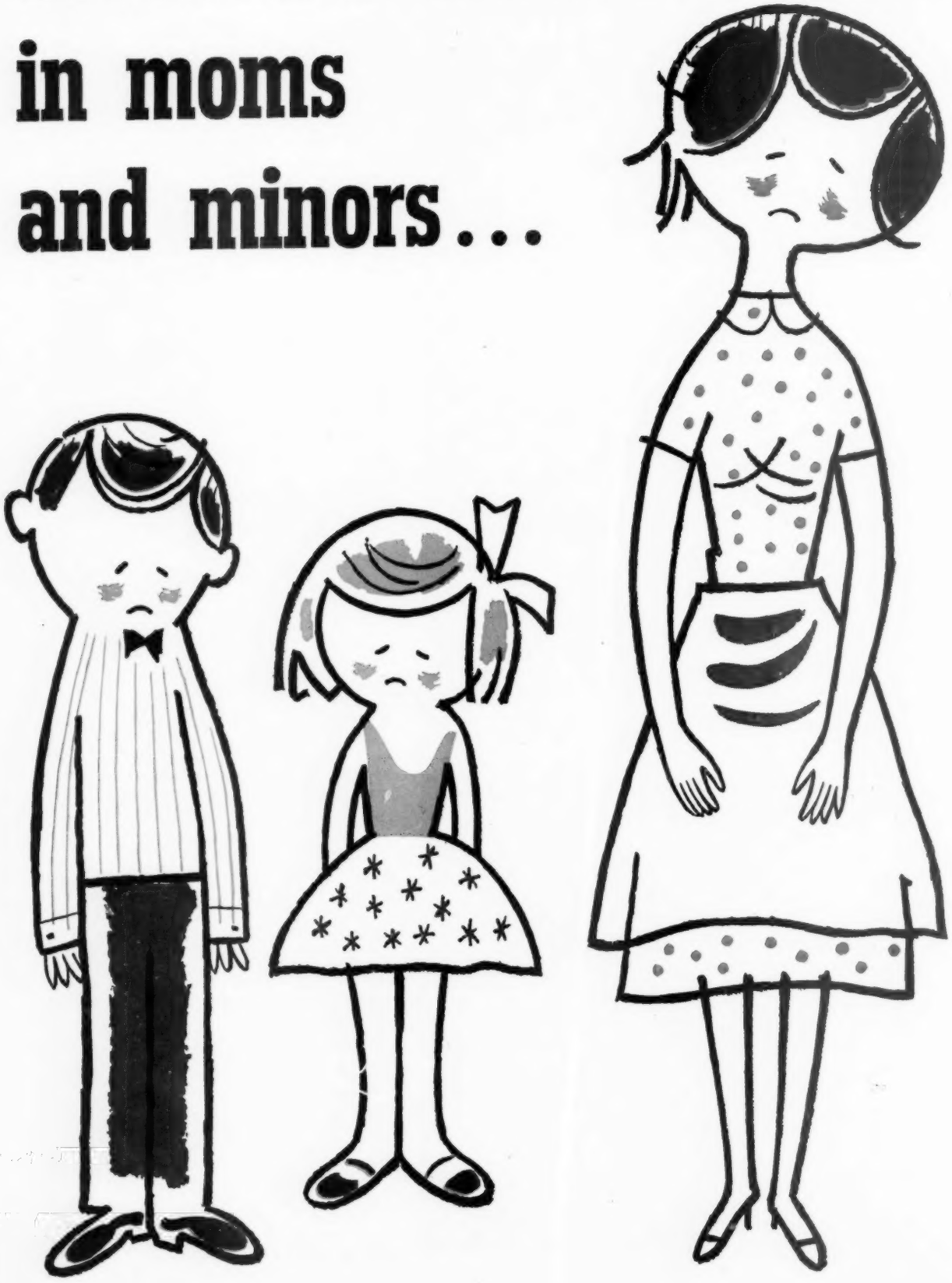
The Upjohn Company, Kalamazoo, Michigan

IRON: often a minus in moms and minors...



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. . . the hematinic with built-in nutritional support

Many growing children and most women of menstrual age deplete their iron reserves and slide into iron-deficiency anemia.

Livitamin changes the minus to a plus because it restores depleted iron reserves and also provides integrated nutritional support.

Iron in Livitamin is well absorbed, with minimum gastric upset and constipation. And with Livitamin there is no worry about teeth stain . . . or taste acceptance.

WRITE FOR LITERATURE
AND DOSAGE INFORMATION.

FORMULA: Each fluidounce contains:

Iron, peptonized (equiv. in elemental iron to 71 mg.)	420 mg.
Manganese citrate, soluble, N.F.	158 mg.
Thiamine hydrochloride	10 mg.
Riboflavin	10 mg.
Cobalamin	20 mcg.
Nicotinamide	50 mg.
Pyridoxine hydrochloride	1 mg.
Pantothenic acid	5 mg.
Liver fraction 1	1 Gm.
Rice bran extract, U.S.P. XIV	1 Gm.
Inositol	30 mg.
Choline	60 mg.

SUPPLIED: *Liquid:* 8 oz. bottles, pints, gallons; *Capsules:* Bottles of 100, 500, 1000. Also available as LIVITAMIN with INTRINSIC FACTOR: bottles of 100 capsules.

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Bristol, Tennessee • New York • Kansas City • San Francisco

■ *"I think that the urine of pregnant mothers should be tested for sugar, but done with the oxidase method, not with other methods, since most of them give you total reducing substances."*

Wilkerson, H. L. C.: Pregnancy and Diabetes, Diabetes, 6:523, 1957.

". . . fetal mortality in the unrecognized diabetic may be as great as, if not greater than, in the known diabetic."[1] Therefore, it is vital to detect abnormal glycosuria during pregnancy.

Because of its greater sensitivity to glucose, Tes-Tape will reveal instances of abnormal glycosuria previously undetected by copper-reduction methods. Also, since Tes-Tape is specific for glucose, it will not give false positive reactions with lactose, galactose, fructose, or other copper-reducing sugars.

Tes-Tape is supplied in handy pocket-size dispensers of approximately 100 tests.

1. Shlevin, E. L.: Pregnancy and Diabetes, Diabetes, 6:523, 1957.

128023

The American Journal of Medicine

VOL. XXXI JULY 1961 NO. 1

Editorial

Fifteen Years of the "Green Journal"

WITH this issue *The American Journal of Medicine* enters its sixteenth year of publication. Fifteen years is a short space of time indeed when compared with the long and distinguished careers of some other medical journals, yet the newcomer with the familiar green cover appears already to have made its impress. It would therefore seem appropriate upon this occasion to examine the present position of the Journal, consider its place in the firmament of medical publications, and review its purpose in the light of current needs in the dissemination of medical knowledge.

The American Journal of Medicine thus far has shown the steady growth expected of a robust adolescent, as the following figures indicate. In its initial year of publication, 1946, the circulation was 1,984, rising to 4,010 within a year, then to 11,323 in five years, and to 15,731 in ten years. The present circulation, in excess of 20,000, is believed to be the largest ever reached in this country by an "independent" medical journal, i.e., one not serving as the organ of a medical organization. There are many indications that even this large figure for paid circulation represents only a fraction of the wide readership of the Journal. Librarians tell us that they are obliged to take more than one subscription to meet the demands of its readers, that the issues are among the most battered by usage, and, alas, the most stolen—sometimes, in fact, the "Green Journal" has to be kept under lock and key. Contributors tell us of requests for reprints in numbers unprecedented in their experience, and from all parts of the world.

When one recalls that *The American Journal of Medicine* does not come gratis to subscribers upon payment of regular society dues, but must be purchased by considered expenditure, this is a gratifying showing indeed. Even more heartwarming is the consideration that, far from catering to superficial tastes or needs, the text of the journal is explicitly directed to the scholarly, the inquiring. That there are so many physicians who somehow find the opportunity to indulge their scholarly inclinations, in the face of all the demands upon their time, is a highly commendatory endorsement of the medical profession at large. It is interesting to note in this connection that a recent survey disclosed that, as often as any other, the "Green Journal" is studied in the quiet of the private or public library, not thumbed through hurriedly in the busy office, and that copies are bound and filed for future reference, not promptly disposed of.

The distribution of *The American Journal of Medicine* deserves comment. Enquiries reveal that an extraordinarily broad cross section of the profession subscribes: general practitioner as well as internist, basic scientist as well as clinical investigator, and the most diverse specialists. It appears to be one of the journals most favored by medical students, interns and residents—and this is no mere coincidence since the journal is intended for serious study of current developments in medical investigation and is, indeed, not infrequently assigned in formal teaching exercises. In this capacity its use is not confined to this country, since there is a large contingent of subscribers and readers from abroad.

This wide acceptance is taken by the Editorial

Board to signify endorsement of the policy of the Journal to strive to maintain the highest possible standards of uncompromising scholarship. To be sure, faithful recording of the growing complexities of clinical investigation inevitably involves the publication of a certain number of very difficult papers which may be impossible for the average reader fully to comprehend (and associated with this, confidentially, there is a certain annual mortality rate, happily not too large, in the subscription lists). Such frustrations, however, seem to be inevitable in modern living. By way of solace it can be said that exposure to new directions of investigation, even if poorly understood, opens up broader perspectives in self-education—healthier insight into our own limitations, if nothing more.

The alternative in editorial policy, to limit its pages to matters of immediate applicability, not only would circumscribe the high purpose of the Journal but would only add to the surfeit of such articles provided by a host of medical publications. Instead, a varied fare is offered, reviews and symposia, editorials and clinicopathologic conferences, case reports and bedside observations as well as more abstruse laboratory investigations in man. It is hoped by this device that in each issue every reader will find something to his taste, and over the years acquire a composite body of information which will be of lasting value. Our eye is to the future as well as to the present.

When *The American Journal of Medicine* was founded in 1946, the country was embarking upon a greatly expanded program of research, made possible by increasing public and private support, and it was anticipated that there might be need for another outlet for publication of results. By helping to make these activities, particularly in our medical schools, research institutes and large teaching hospitals, more widely known it was envisioned that the new Journal might well serve in the furtherance of medical education at all levels. The publication was planned to appear in esthetically pleasing format with distinguished typography. To increase the palatability of the involved expositions that were anticipated a number of pedagogical devices were introduced, such as grouping papers around a common topic instead of publishing in strict chronological sequence of receipt of manuscripts, and insertion into the table of contents of a brief explanation of the pertinence of the article to be presented.

Time has erased the early doubts of the need of addition to what seemed even then to be a plethora of medical journals. The explosion of medical research has, indeed, created many new requirements for fuller circulation of the results of investigation, in volume undreamed of fifteen years ago.

Almost from the start the new Journal received a sufficiency of deserving manuscripts. Before long more were submitted than could possibly be accommodated, an embarrassment of riches that created many problems, the most awkward being the necessity to turn away many worthy papers for sheer stringency of space, and undue delay in publication of accepted manuscripts. Confronted with this dilemma, the publishers gradually expanded the number of pages per issue. In the first year of publication 1,452 pages of text appeared, five years later the annual text was 1,574 pages, in 1956 this grew to 1,978 pages and in 1960 to 2,116 pages. By also introducing a double column format, which increases the wordage per page, and reducing the type size, still however eminently readable, it has thus been possible almost to double the quantity of textual matter per volume. This expansion of text, in the face of steadily mounting printing and production costs which far exceed the subscription price, was accomplished with but one small increase in the cost to subscribers, a feat made possible only by the concomitant increase in advertising in the Journal.

Despite all these exertions it has not been possible to keep up with the ever increasing flood of manuscripts. It is still necessary to return many that are entirely deserving of publication, including some otherwise quite suitable for *The American Journal of Medicine*, and publication still is more delayed than is desirable, although somewhat less than a few years ago. To be sure, this predicament has its consolations; among others, having a wide choice, the opportunity to continue selection solely on the basis of excellence, as judged within the limitations of the reviewers.

The Editorial Board realizes all too well how fallible such judgments must be. Nevertheless, it is quite gratifying, in perusing the pages of *The American Journal of Medicine* over the past fifteen years, to note the sizable proportion of contributions that has stood the test of time, at least over this period. Some papers, it would now appear, stand indeed as landmarks in the recent history of medicine, introducing new

concepts of disease, or new diseases, or new methods of investigation which have proved fruitful. Not the least significant facet of certain of these studies is that at the time of publication they seemed very abstruse indeed and far removed from the exigencies of patient care, yet today they have become part and parcel of our regular medical life. It is such experiences which encourage our faith in the high standards of professional competence in the pages of the Journal, irrespective of the particular area of interest represented.

Needless to say, *The American Journal of Medicine* owes its acceptance to the combined efforts of many persons. Its general editorial policies reflect the attitudes of the distinguished physicians, all seasoned veterans in teaching and investigation, who make up its Editorial Board. Thanks are due not only to its present but also to its past members: S. Howard Armstrong, Jr., David P. Barr, Paul B. Beeson, Francis G. Blake, Arthur L. Bloomfield, Herrman L. Blumgart, Eugene B. Ferris, Jr., Peter H. Forsham, Harry Gold, George H. Houck, Chester S. Keefer, William S. McCann, T. Grier Miller, Jack D. Meyers, Walter W. Palmer, Oswald H. Robertson, Ephraim Shorr, Eugene A. Stead, John W. Taggart, William S. Tillett, Roy H. Turner, Joseph T. Wearn, Russell M. Wilder, Maxwell M. Wintrobe, W. Barry Wood and John B. Youmans. We are further indebted to Carl V Moore for making available the popular Washington University Clinicopathological Conferences appearing in ten issues every year, and to the several editors of the well known Columbia Combined Staff Clinics. Twice a year Guest Editors undertake the organization of symposia, which have attracted such wide attention that they have been made available in separate reprints for more general distribution—to them our gratitude and also to the invited contributors, who have given so unstintingly of their time and effort to further the teaching aims of the Journal. Indeed, a great debt is owing to all of the many authors who have contributed their knowledge to the pages of *The American Journal of Medicine* which, perforce, can be of no higher quality than the quality of the papers of which it is composed. For the arduous task of styling all these manuscripts for publication, responsibility lies in the capable hands of the Managing Editor, Mrs. Helena B. Mannion, to whose zeal so much is due.

Finally, there are our many faithful subscribers and advertisers whose continued support has made this large undertaking possible. To sustain their interest and approbation, it will be the aim of Editorial Board and publishers alike to maintain the high purpose and standards of the "Green Journal."

ALEXANDER B. GUTMAN, M.D.
Editor

Clinical Studies

Serum Lipids, Hypertension and Coronary Artery Disease*

MARGARET J. ALBRINK, M.D.,† J. WISTER MEIGS, M.D. *and* EVELYN B. MAN, PH.D.
New Haven, Connecticut

THE outlook for better health and longer life for our aging population rests, in large measure, upon elimination of vascular disease as a cause of death and disability. Attention has been focused on one after another abnormal lipid factor in the blood of patients with atherosclerosis of the coronary arteries, but the exact nature of the underlying disorder has eluded identification. Upon closer scrutiny, abnormal concentrations of serum cholesterol and various lipoproteins have not proved to be universally present in patients with disease of the coronary arteries; consequently, these factors may be merely inconstant manifestations of a more widespread metabolic defect.

Previous studies from this laboratory established the close association between elevation of serum triglyceride concentration and coronary artery disease [*1–3*]. Recent reports from other laboratories of high serum triglycerides [*4*] and intensified alimentary lipemia [*5*] support this association. Thus a defect in the metabolism of triglycerides, with resultant accumulation of triglycerides in plasma, may be the most common lipid metabolic error in patients with coronary artery disease, and may be the defect basically responsible for many of the other reported lipid manifestations of this disease. The present study confirms and expands studies of serum lipids of normal persons of all ages and of coronary patients. Some light is shed on the relationship of triglyceride concentration to the risk of coronary disease occurring with high serum cholesterol or with hypertension.

MATERIALS AND METHODS

The population under study consisted of apparently normal persons and patients with coronary artery disease. The patients were selected on the basis of previous myocardial infarction diagnosed by unequivocal electrocardiographic evidence and ancillary laboratory data. Approximately 50 per cent of the patients have been mentioned previously [*1,2*]. Almost all were observed in the wards and outpatient clinics of the Yale-New Haven Medical Center. While no effort was made to study all patients with coronary artery disease who were admitted, it is believed that the patients included here constitute a representative sample of the population with coronary artery disease of the past several years, the majority within the past four years.

The 212 patients in this study consisted of 180 males, eight of whom were diabetic. Of the thirty-two female patients, three were diabetic. One hundred and fifteen of the patients were suitable for detailed statistical study, as described later.

The normal control population consisted of 508 apparently healthy persons. Three hundred and ninety seven were men aged twenty to eighty-nine years; included were employees of two New Haven factories, students, university and hospital personnel. One hundred and eleven were women aged twenty to ninety years, chiefly young medical school personnel in their twenties and thirties. The normal persons of both sexes over seventy years of age were residents of a home for the aged, and while all suffered the vicissitudes of old age to some degree, none had diabetes or known coronary artery disease. Details concerning the industrial population will be reported elsewhere [*6*]. Persons who gave a history of coronary artery disease, occlusive vascular disease, diabetes or other metabolic

* From the Department of Internal Medicine and the Department of Epidemiology and Public Health, Yale University School of Medicine, and the Medical Service of the Grace-New Haven Community Hospital, New Haven, Connecticut. This study was supported (in part) by grant H-3498 C2 from the National Heart Institute and grant A-392 C13 from the National Institute of Arthritis and Metabolic Diseases, Bethesda, Maryland.

† This work was performed during tenure of an Established Investigatorship of the American Heart Association. Present address: Department of Medicine, West Virginia School of Medicine, Morgantown, West Virginia.

disorders were excluded. Subjects were not excluded because of hypertension or obesity, but the presence of these conditions was noted.

Blood for serum lipid analysis was drawn with the subjects in the postabsorptive state, between 8 and 9:30 in the morning. Patients were studied at an interval of time after the coronary attack ranging up to twelve years. In some instances two or more studies were made on the same person.

Serum Lipid Studies. Serum lipids of 177 of the 212 patients with coronary artery disease, and of 392 of the 508 normal persons were measured by the methods of Peters and Man [7] as follows: Total fatty acids were determined by titration [8] after extraction with alcohol and ether, saponification, precipitation, washing of the fatty acids and solution in hot alcohol. Cholesterol in the acidified titration mixture was precipitated by the addition of digitonin; the cholesterol digitonide was washed, dried and weighed on a microbalance [9]. Lipid phosphorus was determined using a modification of the Fiske and Subbarow method [10] after digestion of a dried lipid extract with concentrated sulfuric acid, nitric acid and concentrated hydrogen peroxide. Triglyceride fatty acids were calculated by subtracting the cholesterol ester fatty acids, assuming cholesterol to be 72 per cent esterified, and phospholipid fatty acids, estimated as previously described, from the total fatty acids [7]. Triglyceride concentrations are expressed as milliequivalent per liter of triglyceride fatty acids.

The serums of the other thirty-five patients and 116 normal persons were those more recently examined and were analyzed by extraction with 2:1 chloroform methanol, saponification and microtitration of the liberated fatty acids [11]. Cholesterol was determined in the chloroform extract after evaporation of the chloroform and saponification with alcoholic potassium hydroxide by a method differing from that of Abell et al. [12] only by the prior extraction of lipids. Lipid phosphorus was determined essentially as before except that nitric acid was not used in the digestion procedure. Triglyceride fatty acids again were calculated by subtraction of cholesterol ester and phospholipid fatty acids from total titrated fatty acids.

RESULTS

Comparison of Two Methods. Twenty per cent of the serum samples were analyzed by the new method [11] in use for current and future aspects of this study. Comparison of the results obtained by the two methods with each other and with results reported on similar subjects in other laboratories was therefore essential.

Total fatty acids were analyzed both by the method of Man and Gildea [8] and by the method of Albrink [11] and were found to agree satisfactorily [11].

TABLE 1

COMPARISON OF MEAN CHOLESTEROL CONCENTRATIONS IN SERUM OF FIVE DIFFERENT GROUPS OF MEN: THOSE ANALYZED BY THE GRAVIMETRIC METHOD [9], BY THE METHOD OF ABELL ET AL. IN THIS LABORATORY [12], AND BY TWO OTHER GROUPS ALSO USING THE METHOD OF ABELL ET AL. [13,14]

Age (yr.)	Gravimetric		Abell et al. (this lab.)		Lawry et al. [13]		Lewis et al. [14]	
	No.	Mean Cholesterol (mg.%)	No.	Mean Cholesterol (mg.%)	No.	Mean Cholesterol (mg.%)	No.	Mean Cholesterol (mg.%)
20–29...	57	185	9	201	54	212*	129	208
30–39...	50	197	20	214	294	228	341	233
40–49...	79	217	49	242	686	240	391	241
50–59...	68	219	42	240	357	244	291	242
60–69...	49	212	24	239	117	235	116	243

* This figure was for ages twenty-five to twenty-nine.

Total cholesterol determined in the chloroform-methanol extract by the method of Abell et al. [12] was compared with total cholesterol determined by the gravimetric method [9] in 156 serum samples. A variable but fairly consistent difference was noted which appeared to bear a constant relationship to the total cholesterol concentration; the colorimetric method gave results about 10 per cent higher than the gravimetric method. To establish further that a real and predictable difference existed between the two methods, the average cholesterol concentrations of two groups of apparently healthy males were compared. Serum samples from one group were analyzed by the gravimetric method, and serum samples from a second group by the colorimetric method of Abell et al. carried out as already described. Some of the two groups of analyses were performed on the same serum samples and included some of the serum samples of the present study; for the most part, however, the two sets of determinations were made on two different sets of serum samples. The average cholesterol concentrations are given by decade in Table 1, together with similar figures reported by two other groups using the method of Abell et al. [13,14]. It is clear again that the results by the latter method were about 10 per cent higher than those obtained by the gravimetric method. Data based on the method of Abell et al. obtained in this laboratory agreed well with data measured by this method for similar age groups from other parts of the country [13,14].

Because of the demonstrated specificity of the method of Abell et al. [12] and the acceptance of

TABLE II
PER CENT OF ALL PATIENTS SHOWING INCREASED CONCENTRATION OF SERUM TRIGLYCERIDES (5.5 MEQ./L. OR MORE), AT VARIOUS INTERVALS AFTER ACUTE CORONARY OCCLUSION

Time after Acute Episode	Total No. of Patients	Patients with Triglycerides 5.5 mEq./L. or More	
		No.	% of Group
0–7 days.....	62	29	47
8–9 days.....	34	22	65
10–14 days.....	37	28	75
15–30 days.....	38	30	79
1–6 months.....	30	24	80
Over 6 months..	44	36	82

this method as the method of choice by many laboratories, a correction factor of 1.10 was applied to all the cholesterol values determined by the gravimetric method.

Effect of Acute Illness on Lipid Concentrations. Although the patients with coronary artery disease as a group tended to have higher serum triglyceride concentrations than the normal persons, this difference was less marked during the acute phases of illness, in agreement with the observation that acute illness, by virtue of fever, poor dietary intake or other complications of illness [*15*], may reduce circulatory triglycerides. In the absence of repeated studies on the same person at intervals after an acute myocardial infarction, the duration of the effect of acute illness on serum lipids was estimated by a mathematical study of the number of patients with triglycerides exceeding the normal at various intervals after an acute coronary occlusion or after an episode of acute coronary insufficiency. Multiple determinations on some patients were included but no patient was used more than once in any one time period. The results appear in Table II. A triglyceride concentration of 5.5 mEq./L. or above was considered to be elevated on the basis of a previous study [*2*], for reasons to be elaborated subsequently. Despite considerable variation in triglyceride concentration during the first few days after infarction, most serum triglyceride levels were low soon after a myocardial infarction; an increasing number of elevated values occurred during fourteen days after infarction, until by two weeks 80 per cent were elevated. Thereafter there was little change in the proportion of patients with high triglyceride levels. In order to eliminate the depressing effect of acute illness, the remainder of the report will be confined to serum samples examined ten days or more after the acute illness.

Of the 115 non-diabetic male patients studied ten days or more after the attack, five had tendinous xanthomatosis, seven (including two of the patients with tendinous xanthomatosis) had xanthelasma. The remainder of the patients had no known disease which might be associated with a high concentration of serum lipids.

Triglycerides in Serum of Normal Men and Men with Coronary Artery Disease. In Figure 1 is shown by decade the cumulative frequency distribution of the serum triglyceride concentration of normal male adults, and of the 115 male non-diabetic patients with coronary artery disease studied ten days or more after the acute illness. Only one determination per patient was used. In the case of multiple determinations in one patient, the first determination made ten days or more after the acute illness was taken. A vertical line is drawn at a concentration of 5.4 mEq./L. to indicate the upper limit of normal. This figure was based on an analysis of the first 100 patients with coronary artery disease, including those acutely ill, compared with ninety-two apparently normal, predominantly young persons of average age thirty-two (range twenty to eighty-seven years) [*2*]. Although inclusion of more older persons in the normal group and exclusion of the patients acutely ill with coronary artery disease would tend to raise the average triglyceride concentration of both groups, 5.4 has been retained as the most satisfactory dividing point between the population with coronary artery disease and the normal population, as will be elaborated in the discussion.

Figure 1 reveals considerable differences in the serum triglyceride concentrations and in the distribution of these concentrations among apparently healthy men at different ages. In the twenty to twenty-nine year old group only 5 per cent of the subjects had a triglyceride concentration of more than 5.4 mEq./L. This percentage is substantially greater in all older groups; nearly 40 per cent of the 248 men in the forty to sixty-nine year old groups had a triglyceride concentration of more than 5.4 mEq./L. However, of thirteen men seventy years old or over, only two had a triglyceride concentration over 5.4 mEq./L.

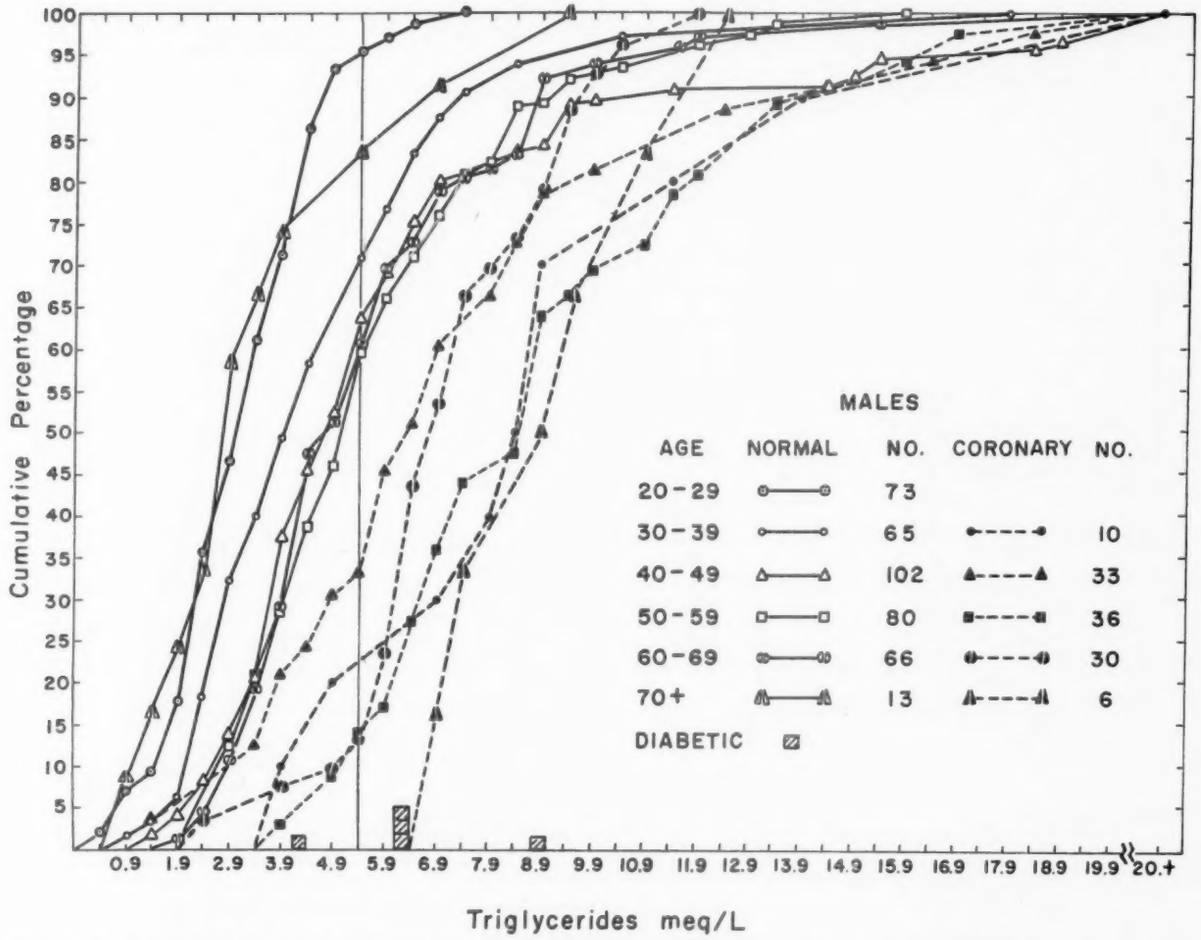


FIG. 1. Cumulative frequency distribution of serum triglyceride concentration of normal men and male patients with coronary artery disease, by decade. Patients studied less than ten days after the acute coronary episode are not included. The triglyceride concentrations of the five male diabetic patients are not included in the curves but are indicated by squares along the base line. A vertical line at 5.4 mEq./L. indicates the upper limit of normal of triglyceride concentration.

The distribution curves for the patients with coronary artery disease, shown as dotted lines for each decade in Figure 1, fell at higher concentrations of triglyceride than those for the normal groups at all ages and at all but the extreme upper range of the distribution. The most marked difference between the normal population and the population with coronary artery disease is seen between the normal men aged twenty to twenty-nine years and the patients with coronary artery disease of all ages, but the difference is also clear decade by decade despite the increasing number of normal subjects exceeding the established upper limit of normal. The serum triglyceride concentration of the patients with coronary artery disease in the fifth decade of life was the least high of the patients, and also the least different from those of the normal groups of the same age. The greatest differences were found beyond age fifty. Considering together the ages forty to sixty-nine, when the distribution curves were almost identical in the normal population, the concentration of triglycerides was 5.5 or more in 38 per cent of the normal subjects and in 82 per cent of the patients with coronary artery disease.

Cholesterol Concentration in the Serum of Normal Men and Men with Coronary Artery Disease. Figure 2 depicts the cumulative frequency distribution of the serum cholesterol concentration in normal subjects and in patients with coronary artery disease by decade. A vertical line is drawn at a concentration of 260 mg. per cent to facilitate the comparison of normal subjects and those with coronary artery disease of various ages with respect to the fraction of each population group

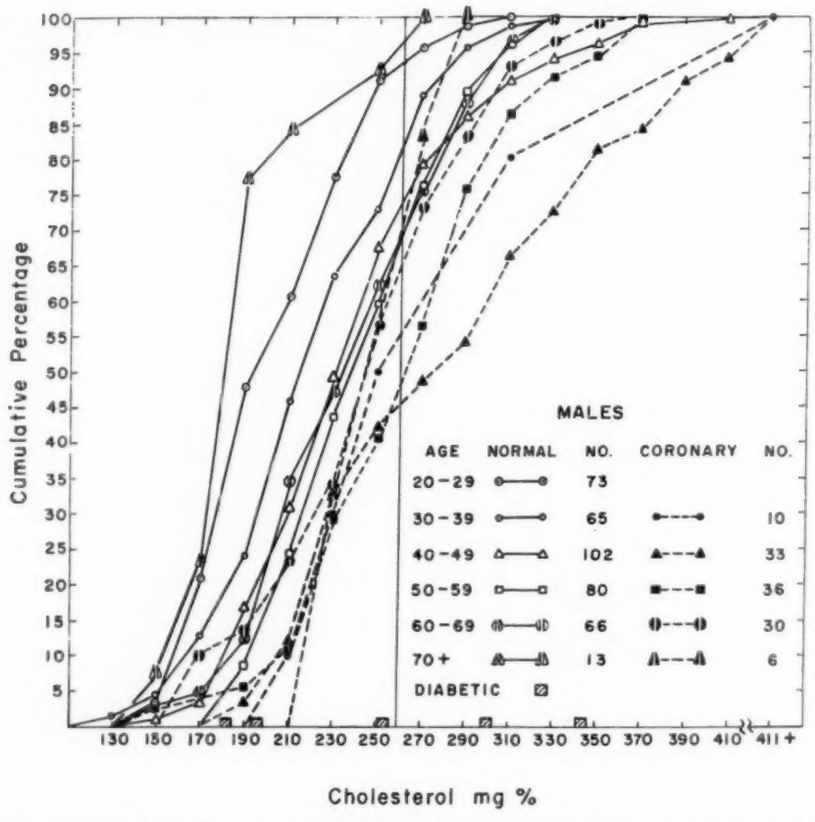


FIG. 2. Cumulative frequency distribution of serum cholesterol concentration of normal men and male patients with coronary artery disease by decade. Patients studied less than ten days after the acute coronary episode are not included. The cholesterol concentration of the serum of five diabetic patients is shown on the base line by squares. A vertical line at 260 mg. per cent indicates the upper limit of normal.

exceeding this upper limit of selected normals. In consideration of the definition of "normal," the concentration permitting the separation of the normal subjects from the persons with coronary artery disease with the fewest number of misclassifications was 234 mg./100 ml., when based on the same preliminary populations as used to set the upper limit of normal for serum triglycerides. While this figure would be expected to provide the best statistical separation, the overlap was so great that this figure could have little meaning in an individual case. It was exceeded by 20 per cent of the normal men in their twenties, by 50 per cent of the normal population aged forty to sixty-nine, and by about 65 per cent of the population with coronary artery disease. Two hundred and sixty milligrams per cent was chosen as a more meaningful concentration with which to compare the normal groups and the groups with coronary artery disease for the following reasons: This is the concentration above which the Framingham study [*16*] revealed a marked increase in risk of coronary artery disease. Furthermore, only 5 per cent of normal men in their twenties had serum cholesterol concentrations above this figure, and the serum triglyceride concentration of 5.4 mEq./L. had been selected on a comparable basis, that it was exceeded by only 5 per cent of normal men.

The serum cholesterol concentration of the normal men was higher in each successive decade until age fifty. Thereafter it was similar in the next three decades. After age seventy, low concentrations once more predominated. Although the serum cholesterol concentration of the patients with coronary artery disease was generally higher than that of the normal subjects, it is readily apparent from inspection of Figures 1 and 2 that neither the over-all separation of the population with coronary artery disease and the normal population nor the difference between normal subjects and those

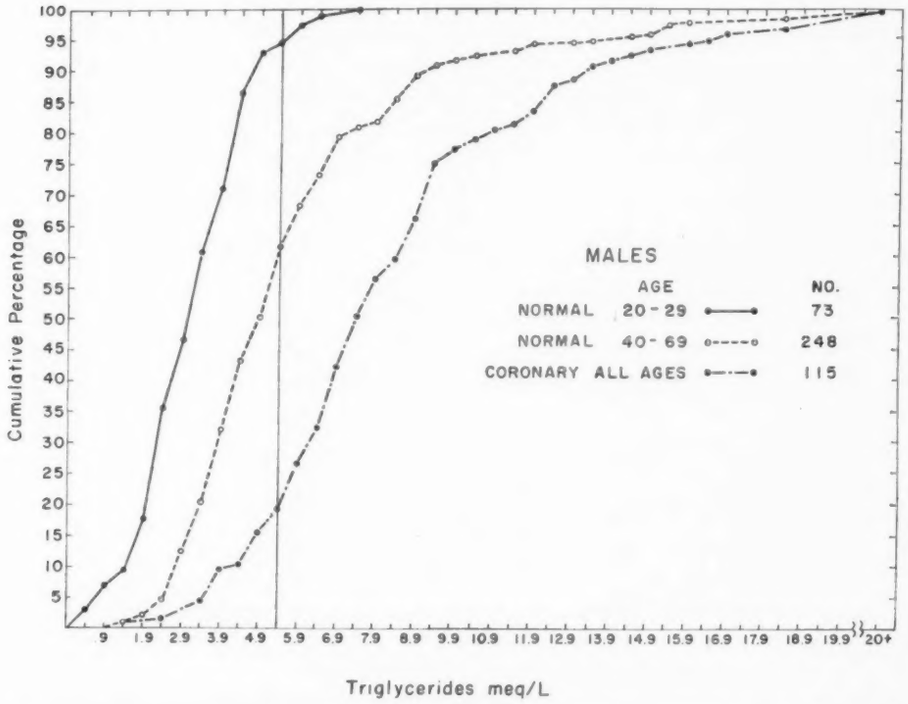


FIG. 3. Cumulative frequency distribution of serum triglyceride concentration of normal men aged twenty to twenty-nine, normal men aged forty to sixty-nine, and patients of all ages with coronary artery disease.

with coronary artery disease of the same age is as clear as was the case with serum triglycerides. The rather unimpressive differences between the two groups in the thirties and forties virtually disappear in the fifties and sixties, at a time when coronary artery disease takes its greatest toll. The difference reappears in the seventies by virtue of the low concentration in the serum of the normal persons of this age group. Although the groups in this age bracket are small, there appears to be a considerable difference between normal men of seventy years or older and those who have coronary artery disease. Only one of thirteen of the normal men had a serum cholesterol level over 260 mg. per cent, whereas two of six patients had higher concentrations. Over age seventy the median concentration was about 175 mg./100 ml. for normal men compared to about 245 mg./100 ml. for the patients.

For greater clarity of presentation the information contained in Figures 1 and 2 is presented in condensed form in Figures 3 and 4. The number of distribution curves for normal men is reduced to two, one for ages twenty to twenty-nine (the group with the lowest serum triglyceride and cholesterol concentrations) and a second curve for ages forty to sixty-nine, when the highest serum lipid concentrations occurred. A third curve represents patients of all ages with coronary artery disease. The difference between serum triglyceride concentrations of patients

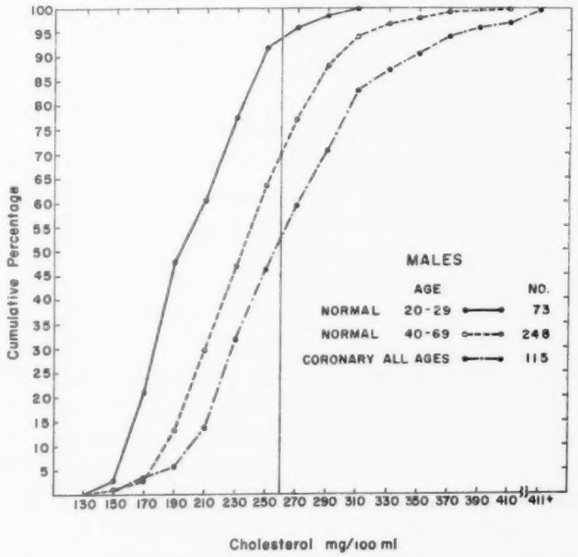


FIG. 4. Cumulative frequency distribution of serum cholesterol concentration of normal men aged twenty to twenty-nine, normal men aged forty to sixty-nine, and patients of all ages with coronary artery disease.

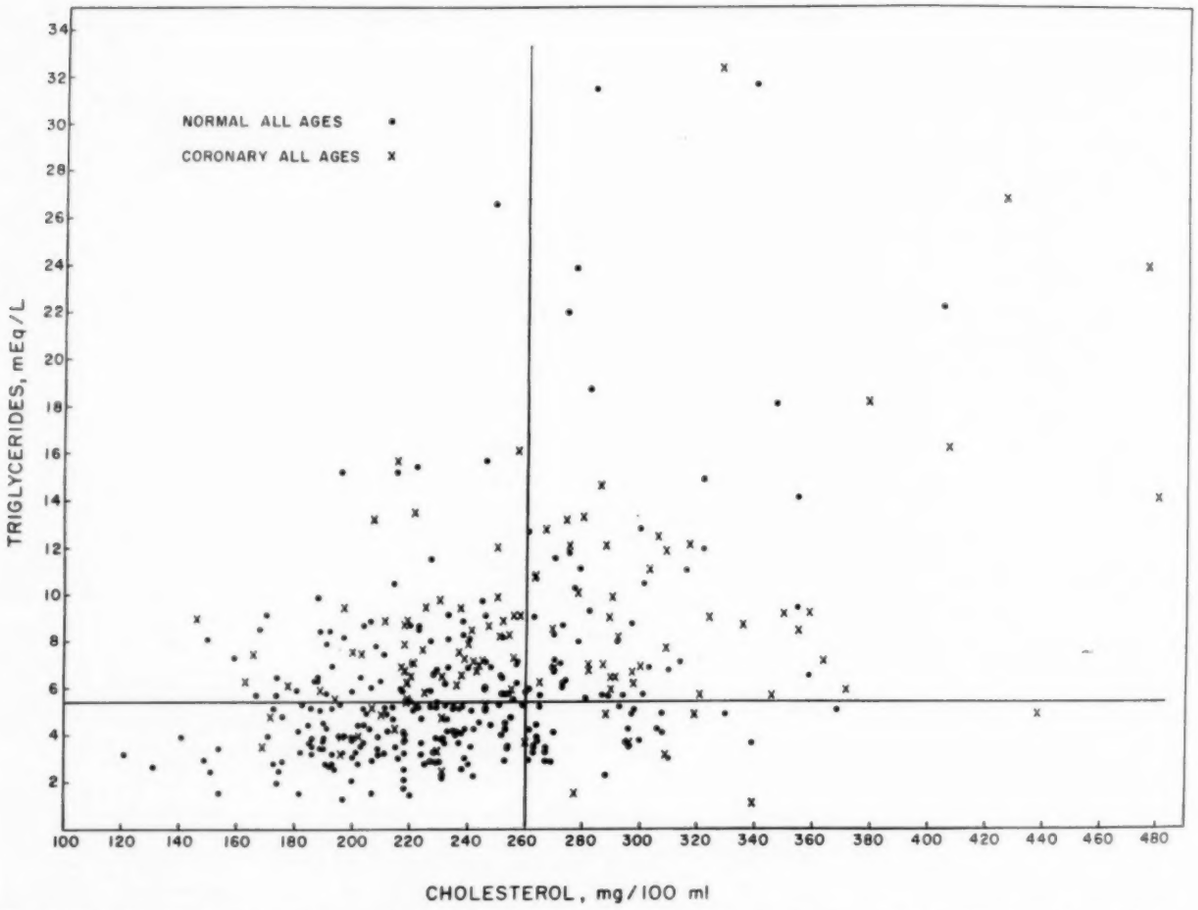


FIG. 5. Relationship between concentrations of cholesterol and triglycerides in the serum of 250 normal men aged thirty to sixty-nine, and of 115 patients with coronary artery disease.

and normal persons is clearly evident with respect to either the young or older group. A comparison of Figures 3 and 4 plainly reveals a greater percentile spread between the serum triglyceride concentrations of the normal groups and the groups with coronary artery disease than between the serum cholesterol concentrations of the two groups.

Comparison of Serum Cholesterol and Triglyceride Concentrations in the Normal Population and in the Population with Coronary Artery Disease. The relationship between serum cholesterol and triglyceride concentrations is shown in a scattergram in Figure 5. Triglycerides and cholesterol appear as relatively independent variables with little or no correlation at the concentrations observed in this study. For example, there are normal subjects with serum cholesterol concentrations as high as 340 mg. per cent and serum triglycerides as low as 3.5 mEq./L. Conversely, subjects with serum cholesterol concentrations as low as 140 mg. per cent had high serum triglyceride concentrations. (Fig. 5.) In Table III the association of high cholesterol and high triglyceride concentrations is represented in the following way: In the first column headed "per cent" are listed by per cent the number of persons in each age group whose serum cholesterol concentrations were elevated above 260 mg./100 ml. but whose triglycerides were normal. The second "per cent" column contains in per cent subjects with abnormally high concentrations of both cholesterol and triglycerides. In the third "per cent" column are the persons with normal serum cholesterol concentrations but increased triglycerides. In the last two columns appear the number and per cent with increased serum concentrations of either cholesterol, triglycerides or both. The total per cent with high cholesterol can be calculated by adding the first and second per cent groups, the total with high triglycerides by

TABLE III

PER CENT OF NORMAL MEN AND OF MALE PATENTS WITH HIGH CONCENTRATIONS OF SERUM TRIGLYCERIDES (5.5 MEQ./L. OR MORE), OR SERUM CHOLESTEROL (260 MG./100 ML. OR MORE), OR BOTH (DIABETIC PATIENTS OR PATIENTS STUDIED PRIOR TO TEN DAYS AFTER THE ACUTE ILLNESS WERE EXCLUDED)

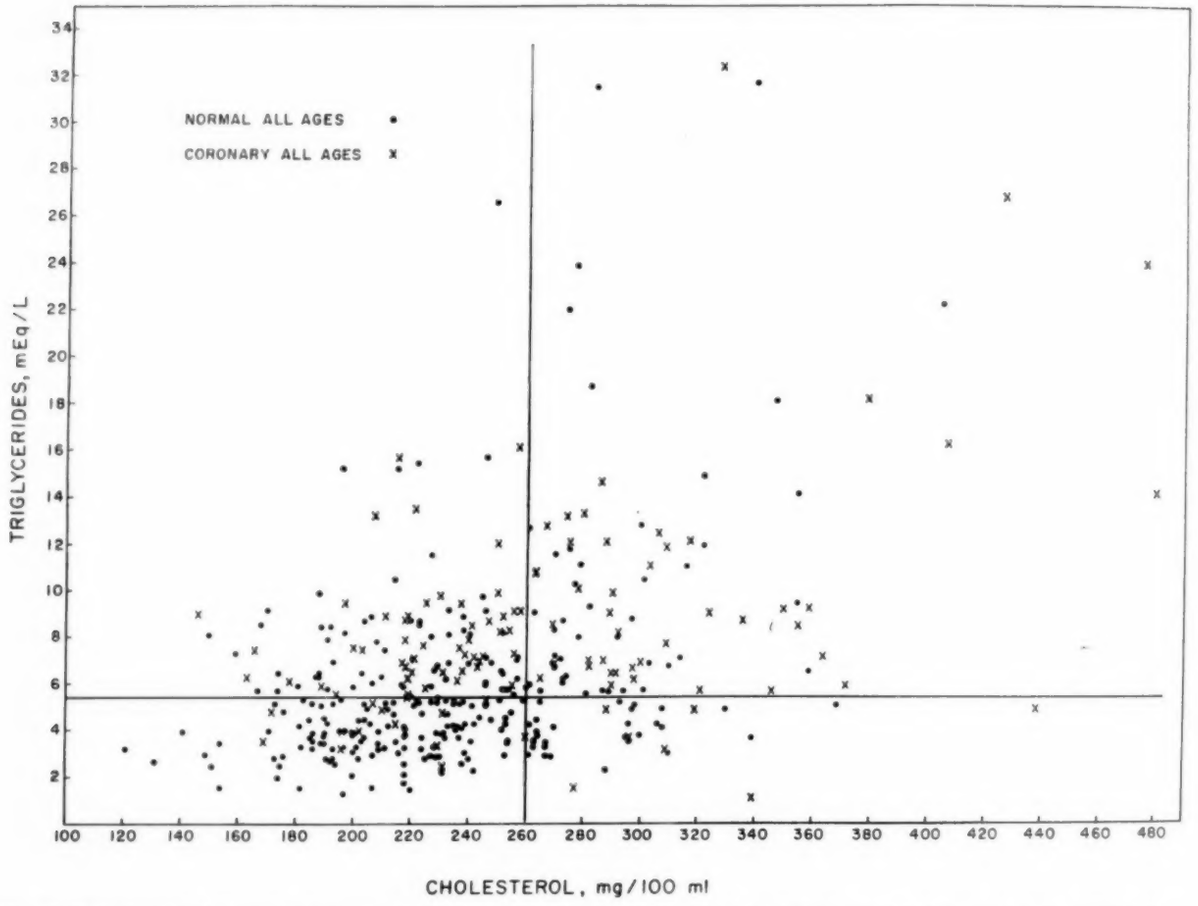
Age (yr.)	Total No.	Cholesterol > 260 mg. % Triglycerides < 5.5 mEq./L.		Cholesterol > 260 mg. % Triglycerides > 5.5 mEq./L.		Cholesterol < 260 mg. % Triglycerides > 5.5 mEq./L.		Total with One or Both High	
		No.	%	No.	%	No.	%	No.	%
Normal Subjects									
20–29.....	73	3	4	1	1	3	4	7	10
30–39.....	65	7	11	5	8	14	22	26	40
40–49.....	102	12	12	17	17	20	20	49	48
50–59.....	80	10	13	13	16	19	24	42	53
60–69.....	66	7	11	12	18	14	21	33	50
70 +.....	13	1	8	0	0	2	15	3	23
All ages excluding 20–29...	326	37	11	47	15	69	21	153	47
Patients with Coronary Artery Disease									
20–29.....	...	...	...	...	...	...	...	...	...
30–39.....	10	1	10	4	40	4	40	9	90
40–49.....	33	5	15	13	39	9	27	27	82
50–59.....	36	0	0	18	49	14	38	32	86
60–69.....	30	1	3	8	27	18	60	27	90
50 +.....	6	0	0	3	50	3	50	6	100
All ages...	115	7	6	46	40	48	42	101	88

adding the second and third groups (or by reference to Figures 1 and 2).

Only 10 per cent of the normal male population aged twenty to twenty-nine had high serum triglycerides, high cholesterol levels or both. This figure was increased to 47 per cent for ages thirty and above. The 47 per cent group was composed of 36 per cent with high serum triglycerides with or without high serum cholesterol levels, and 11 per cent who had only high cholesterol levels. Slightly less than half of those with high serum triglycerides had associated high serum cholesterol levels.

In the lower part of Table III it may be seen than 82 per cent of the patients of all ages with coronary artery disease had high serum triglyceride concentrations; about half of them also had high cholesterol levels. In an additional 6 per cent the serum cholesterol level was increased without a concomitant increase in triglycerides. Elevation of serum cholesterol in the absence of elevated triglyceride values characterized only about 10 per cent of the normal population, 10 to 18 per cent of the patients with coronary artery disease under fifty years of age, but virtually none of the patients over age fifty.

Fifteen of the 115 patients had neither high serum triglycerides nor high serum cholesterol levels, nor was there a tendency for either to be near the upper limit of normal: For the fifteen subjects, the serum cholesterol concentrations ranged from 169 to 246 mg./100 ml., only four being over 220. The serum triglycerides ranged from 2.4 to 5.3 mEq./L.; four were over 5 mEq./L. Possibly of significance is the time of examination: Seven of the fifteen were studied between ten days and two weeks after the acute



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		No.	%	No.	%	No.	%	No.	%
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20–29.....	73	3	4	1	1	3	4	7	10
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All ages excluding 20–29...	326	37	11	47	15	69	21	153	47
Patients with Coronary Artery Disease									
20–29.....	...	...	...	...	...	...	...	...	...
30–39.....	10	1	10	4	40	4	40	9	90
40–49.....	33	5	15	13	39	9	27	27	82
50–59.....	36	0	0	18	49	14	38	32	86
60–69.....	30	1	3	8	27	18	60	27	90
50 +.....	6	0	0	3	50	3	50	6	100
All ages...	115	7	6	46	40	48	42	101	88

adding the second and third groups (or by reference to Figures 1 and 2).

Only 10 per cent of the normal male population aged twenty to twenty-nine had high serum triglycerides, high cholesterol levels or both. This figure was increased to 47 per cent for ages thirty and above. The 47 per cent group was composed of 36 per cent with high serum triglycerides with or without high serum cholesterol levels, and 11 per cent who had only high cholesterol levels. Slightly less than half of those with high serum triglycerides had associated high serum cholesterol levels.

In the lower part of Table III it may be seen than 82 per cent of the patients of all ages with coronary artery disease had high serum triglyceride concentrations; about half of them also had high cholesterol levels. In an additional 6 per cent the serum cholesterol level was increased without a concomitant increase in triglycerides. Elevation of serum cholesterol in the absence of elevated triglyceride values characterized only about 10 per cent of the normal population, 10 to 18 per cent of the patients with coronary artery disease under fifty years of age, but virtually none of the patients over age fifty.

Fifteen of the 115 patients had neither high serum triglycerides nor high serum cholesterol levels, nor was there a tendency for either to be near the upper limit of normal: For the fifteen subjects, the serum cholesterol concentrations ranged from 169 to 246 mg./100 ml., only four being over 220. The serum triglycerides ranged from 2.4 to 5.3 mEq./L.; four were over 5 mEq./L. Possibly of significance is the time of examination: Seven of the fifteen were studied between ten days and two weeks after the acute

TABLE IV

PER CENT OF NORMAL MEN WITH AND WITHOUT HYPERTENSION SHOWING INCREASED CONCENTRATION OF SERUM CHOLESTEROL (260 MG. PER CENT OR MORE), TRIGLYCERIDES (5.5 MEQ./L. OR MORE) OR BOTH

Age (yr.)	Total No.	Cholesterol > 260 mg. % Triglycerides < 5.5 mEq./L.		Cholesterol > 260 mg. % Triglycerides > 5.5 mEq./L.		Cholesterol < 260 mg. % Triglycerides > 5.5 mEq./L.		Total with One or Both High	
		No.	%	No.	%	No.	%	No.	%
Normal Men with Normal Blood Pressure									
30–39	38	4	11	4	11	10	26	18	47
40–49	75	8	11	14	19	17	23	39	52
50–59	57	5	9	11	19	13	23	29	51
60–69	37	4	11	7	19	8	22	19	51
Total all ages	207	21	10	36	17	48	23	105	50
Normal Men with High Blood Pressure									
30–39	2	0		0		1	50	1	50
40–49	5	1	20	1	20	1	20	3	60
50–59	13	2	15	1	8	5	38	8	61
60–69	19	2	11	4	21	5	26	11	58
Total all ages	39	5	13	6	15	12	31	23	59

myocardial infarction when the effects of acute illness might still have had a lowering effect. (Table II.) Nine of ten whose habits were known smoked. Three of the fifteen were hypertensive, about the same fraction as found in the normal population. Serum cholesterol and triglyceride levels in one were normal at two months but abnormal one and two years after the infarction, although in two other patients serum cholesterol and triglycerides were consistently normal upon re-examination at later dates. These patients ranged from thirty-nine to sixty-eight years of age. A small group of patients apparently had normal serum lipids at all times.

Relationship of Serum Lipids to Blood Pressure. Blood pressure data were available for 246 of the normal men aged thirty or over, and for all patients with coronary artery disease. Hypertension was defined as a systolic pressure of 160 mm. Hg or above, or a diastolic pressure of 100 mm. Hg or above, or both. If a patient with coronary artery disease had a history of documented hypertension prior to the attack he was classed as hypertensive without regard to blood pressure readings during the acute illness. In most instances hypertension was documented by multiple readings, but in some instances only a single reading was available. The levels chosen were those classified as marked elevation of blood pressure in the Framingham study and found to be associated with increased risk of coronary artery disease [*16*].

Table IV compares the serum lipids of normal men who had normal blood pressures, with the lipids of otherwise normal men with hypertension. Sixteen per cent of the total number of normal subjects had hypertension; most of them were fifty to sixty-nine years old. Fifty-nine per cent of all hypertensive normal men had an increase in serum triglycerides, cholesterol or both, as opposed to increased triglycerides or cholesterol for 50 per cent of normotensive normal men over thirty. Thus there was only a slight tendency for hypertensive normal men to have higher serum lipids than normotensive men, and nearly half the hypertensive normal men had normal lipids. Table V gives data relative to hypertension for 115 men who have had myocardial infarctions. Twenty-nine per cent of the 115 patients with coronary artery

TABLE V

PER CENT OF MEN WITH CORONARY DISEASE WITH AND WITHOUT HYPERTENSION SHOWING INCREASED CONCENTRATION OF SERUM CHOLESTEROL (260 MG. PER CENT OR MORE), TRIGLYCERIDES (5.5 MEQ./L. OR MORE), OR BOTH

Age (yr.)	Total No.	Cholesterol > 260 mg. % Triglycerides < 5.5 mEq./L.		Cholesterol > 260 mg. % Triglycerides > 5.5 mEq./L.		Cholesterol < 260 mg. % Triglycerides > 5.5 mEq./L.		Total with One or Both High	
		No.	%	No.	%	No.	%	No.	%
Patients with Coronary Disease with Normal Blood Pressure (Males)									
30–39.....	10	1	10	4	40	4	40	9	90
40–49.....	27	3	11	11	41	9	33	23	85
50–59.....	26	0		14	54	7	27	21	81
60–69.....	15	0		3	20	10	67	13	87
70 +.....	4	0		2	50	2	50	4	100
Total all ages.....	82	4	5	34	42	32	39	70	85
Patients with Coronary Disease with High Blood Pressure (Males)									
30–39.....	0								
40–49.....	6	2	33	2	33			4	67
50–59.....	10	0		4	40	6	60	10	100
60–69.....	15	1	6	5	33	8	53	14	93
70 +.....	2	0		1	50	1	50	2	100
Total all ages.....	33	3	9	12	36	15	45	30	91

disease had hypertension; the proportion increased with age to a high of 50 per cent in the sixties. Of the hypertensive patients, 91 per cent had elevated serum cholesterol or triglycerides or both. This percentage is comparable to the 85 per cent of non-hypertensive patients with coronary artery disease who had high serum lipids. Only 9 per cent of the hypertensive patients had normal serum lipids in contrast to the 41 per cent of the hypertensive normal men who had normal lipids.

Diabetes. Five diabetic subjects were not included in the distribution curves or in the tables but are shown separately in Figures 1 and 2. Both their serum triglyceride and cholesterol concentrations were entirely comparable to those of the non-diabetic patients with coronary artery disease.

Coronary Disease in Women. Serum lipid data were available for twenty-three women who had suffered myocardial infarctions. The women, three of whom had diabetes, ranged in age from twenty to seventy-two years; the seventh decade had the highest number for any ten year span. In relation to the small numbers of normal women over thirty years of age and the seeming lack of an age trend in the concentration of their serum lipids, the frequency distribution of the triglycerides and the cholesterol of the serum of normal women of all ages are compared in Figures 6 and 7 with similar curves for the women of all ages with coronary artery disease. The normal women appear to resemble normal young men with respect to serum lipid concentrations, although further studies of older women may reveal higher lipids in older age groups, as reported by others [*13,14*]. The serum lipids of women who had had myocardial infarctions are entirely comparable to those of men with this disease.

Cholesterol:Phospholipid Ratio. General recognition that the serum cholesterol concentration is only suggestively correlated with coronary artery disease has prompted a search for abnormal interrelations between serum lipid fractions as the factor associated with coronary

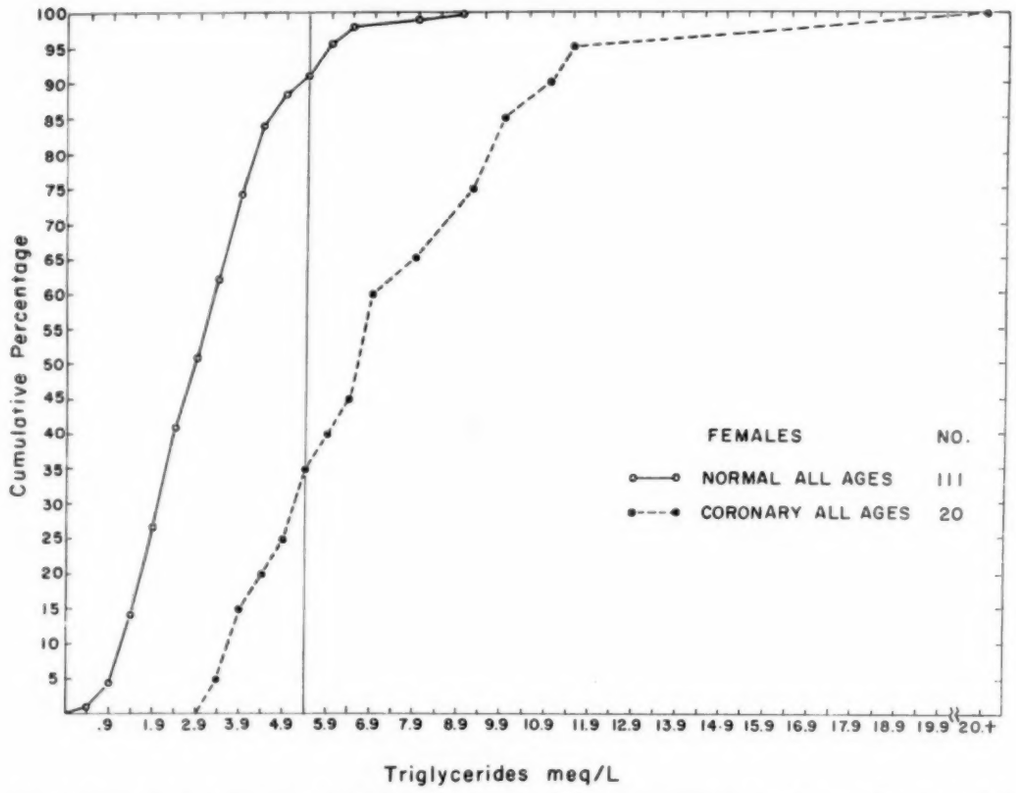

FIG. 6. Cumulative frequency distribution of serum triglyceride concentration of normal women and female patients of all ages with coronary artery disease. Patients studied less than ten days after the acute coronary episode and diabetic patients are not included.

artery disease. An increase in the cholesterol: phospholipid ratio had been reported to occur in disease of the coronary arteries [*17*], but in the present study appeared merely to reflect the concentration of serum total cholesterol in a vague way, and to bear no more relationship to the disease than the serum cholesterol itself. Therefore graphs and mathematical data are not included.

Normal Variation in Serum Lipids. The significance of a single serum triglyceride concentration must, of course, be interpreted in relation to technical and biological variation. The technical error is not negligible, since it must reflect the cumulative errors of three methods. Multiple studies of single subjects over a period of years revealed considerable individual variation [*7,18*]. In 100 unselected consecutive analyses [*6*] the technical error of serum triglyceride determinations calculated by the following formula

$$\text{T.E.} = \sqrt{\frac{S\Delta 2}{N \times 2}}$$

where $S\Delta$ is the sum of differences between duplicate analyses, and N is the number of pairs [*13*], was 0.45 mEq./L. when the total triglyceride concentration was less than 10 mEq./L. and somewhat higher, 0.81, when the triglycerides were between 10 and 96 mEq./L. The biological variation, which is somewhat greater, was determined for eighty men using the same formula, except that Δ = difference between two different serum specimens obtained from the same person on two different occasions six months to two years apart [*6*]. The biological error so measured was 1.2 mEq./L. when the total triglyceride concentration was under 10, and 3.2 mEq./L. when the triglyceride content was over 10 mEq./L. In view of the T.E. alone it might be wise, therefore, to add at least 1 mEq./L. (2 × T.E.) to the concentration of 5.5 mEq./L. before classifying a serum triglyceride concentration as abnormally high on the basis of a single determination.

As a group, the normal men mentioned in the last paragraph had an over-all 7 per cent difference in the per cent with serum triglyceride concentrations over 5.4 mEq./L. on two testing

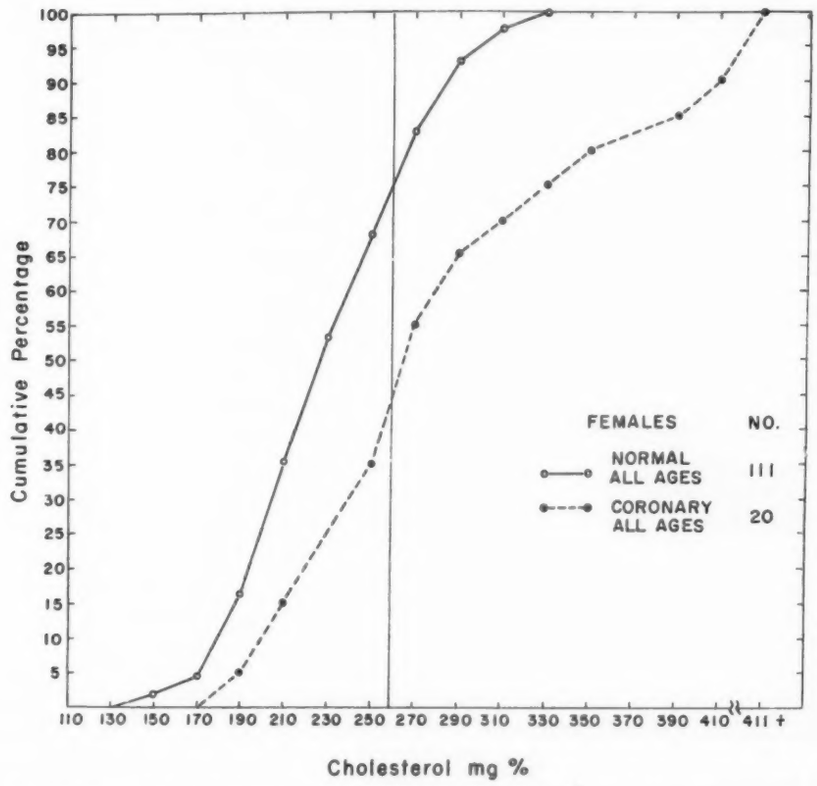

FIG. 7. Cumulative frequency distribution of serum cholesterol concentration of normal women and female patients of all ages with coronary artery disease. Patients studied less than ten days after the acute coronary episode and diabetic patients are not included.

occasions, although there was considerable individual variation in this respect [*6*]. Therefore, for one group to differ from another with respect to per cent of those with elevated serum triglyceride concentration, a difference of at least 7 per cent between the two groups must occur. The percentage of patients with high serum triglycerides did not differ by more than 7 per cent when comparisons were made between patients receiving low fat (60 gm. a day or less) or low calorie (1,200 calories a day or less) diets and those receiving regular diets; between smokers and non-smokers; or between patients receiving anticoagulants and those not receiving them.

COMMENTS

The serum triglyceride levels in this series appeared to provide a better separation between normal persons and patients with coronary artery disease than the reported measurements of other serum lipids, and may provide the most accurate single indication yet available of the biochemical lipid defect recognizable in disease of the coronary arteries. The difficulty with most factors previously investigated has been that too small a proportion of patients with coronary artery disease exhibit the attribute in question, while too many of the normal population have the same attribute. Some attributes, such as elevated serum cholesterol levels, appear to be of significance only in relatively young adults and offer no differential help in subjects over the age of fifty, when coronary disease usually occurs. The serum triglyceride concentration provides its best differentiation in those over age fifty. A recent report from another laboratory has confirmed the finding of elevation of serum triglycerides in patients with coronary artery disease [*4*]. These observations merit major consideration in an era when serum lipid and lipoprotein studies are assuming increasing significance in the field of public health [*19*].

To be diagnostic of coronary artery disease susceptibility, a serum component serving as a criterion must meet certain requirements.

There must be a critical concentration which is surpassed by most patients with coronary artery disease and, to be of predictive value, it must also be surpassed by that proportion of the "normal" population of a given age who may either have or may be expected to have coronary artery disease. The normal population must not have the attribute in a concentration above the critical value.

The serum triglycerides were increased in 82 per cent of all the patients studied ten days or more after a coronary attack (Table III), when the effects of acute illness on serum lipids had subsided. (Table II.) After the age of fifty, 89 per cent or more of patients had high serum triglycerides. A retrospective study such as this cannot state whether the increase in triglycerides existed before the development of overt coronary disease, but it has been found in the Framingham study [*20*] that the serum cholesterol and lipoproteins studied after coronary occlusion were essentially unchanged from the concentration in the serum of the same subjects before the attack. There is some evidence that serum lipoprotein concentrations are related to serum triglycerides, as will be mentioned subsequently and described in more detail elsewhere [*21*]. If impairment of triglyceride metabolism is associated with coronary artery disease, increased serum triglyceride may be comparable before and after a myocardial infarction, apart from the period of acute illness.

Elevated serum triglyceride concentration is therefore present in a statistically meaningful per cent of patients with coronary artery disease. The next criterion to be met is the presence of high serum triglycerides in that part of the normal population which will develop or is now harboring the disease in question. In the absence of a long term longitudinal study, the patient with clinically inapparent coronary artery disease cannot be identified; as a second approximation, the per cent of "normal" persons with high serum triglycerides must approximate the per cent which may reasonably be expected to be harboring the disease at any given age. The prevalence rate of arteriosclerotic heart disease increases with age from about 5/1,000 men aged thirty to thirty-four [*16*] to a range between 36 and 46/1,000 in middle-aged men [*16,22–24*]. Thus only about 4 per cent of a given middle-aged population has diagnosed coronary heart disease at a given time. However, that disease of the coronary arteries may be expected to develop in a large proportion of the remainder is clear from the incidence rate of about 1/1,000 men per year for men under forty, increasing to 15/1,000 over age forty-five [*16*] and as high as 29/1,000 per year for men fifty-five to seventy [*22*]. Both the incidence and prevalence of coronary heart disease thus increase markedly at about age fifty and continue over the next twenty years or so. That roughly one-third to one-half of middle-aged men will die of coronary artery disease implies that far more are harboring the disease than can be ascertained from the prevalence of diagnosed disease.

The serum triglyceride concentrations in "normal" men of the present study were increased above normal in about 40 per cent over the age of forty, entirely in keeping with the proportion which might be expected to be harboring the disease and in whom overt manifestations of coronary occlusion will eventually develop. The marked rise in serum triglyceride concentration with age occurring in the thirties and forties precedes by about twenty years the peak incidence of coronary artery disease in the fifties and sixties. This is consistent with the hypothesis of a slowly developing chronic process of which elevation in triglycerides may be the first detectable evidence in serum.

The final requirement for a prognostic serum indicator is that the normal population does not have the attribute in question. The possibility that "normal" middle-aged men may have undiagnosed coronary disease precludes the possibility of using them as representatives of a population free of the disease. Fatty streaks occur in aortas of persons of all ages from infancy on [*25*], and coronary disease may occur in young adults. However, among adult men, those in early adulthood are least likely to be harboring coronary disease. This group, then, was chosen as the normal population with which the effects of both age and disease could be compared, although the argument that standards for the healthy middle aged may be obtained from the young age group cannot at the moment be more than merely plausible. The serum triglyceride concentration adequately fulfills the third criterion: that a normal population does not have the diagnostic attribute in question. The critical concentration of 5.4 mEq./L. was exceeded by only 5 per cent of normal men twenty to twenty-nine years of age. This young group had a mean serum triglyceride concentra-

tion of 3 mEq./L., with a standard deviation of 1.5 mEq./L. Antonis and Bersohn have found even lower mean concentrations of serum triglycerides in young men [*4*]. The concentration of 6 mEq./L. (the mean plus 2 standard deviations) which should theoretically be exceeded by only 2.5 per cent of the normal population of this age is technically and biologically compatible with the critical concentration of 5.5 mEq./L. This observation gives added support to the choice of the latter figure as the dividing point between normality and coronary susceptibility.

A further justification for choosing serum lipids of young adults as "normal" concerns the nature of the increase in lipid concentration observed with increasing age. Although the present study demonstrates a rather marked increase in serum triglyceride concentration in older age groups, such a rise may not be an obligatory consequence of aging in all subjects. The increase in serum cholesterol concentration with age is known to occur only in some but not all subjects; the mean rise with age thus reflects the influence of only some persons rather than an obligatory increase with age in all persons [*26–28*]. The tendency for the serum triglyceride concentration of persons over seventy to be similar to the concentration in normal twenty to twenty-nine year olds (Fig. 1) suggests that by age seventy all or most persons with high serum triglycerides and a tendency for coronary artery disease have died from this disease. Those who are still living may be those whose serum triglyceride concentrations have not changed appreciably since early adulthood. Relative to this possibility is the slightly lowered risk of coronary disease of subjects beyond the age of seventy [*29*].

The serum triglyceride concentration, then, appears to offer a reasonable means of separating the population with coronary artery disease from the normal population.

As corroborative evidence, non-pregnant women of all ages have lower serum triglyceride concentrations than do men, in agreement with their lower susceptibility to coronary disease [*30*]. (Figs. 6 and 7.) Of women in whom coronary disease does develop, however, about the same proportion exhibited increased serum triglycerides as did male patients with coronary disease. (Fig. 6.)

Serum Cholesterol Concentration. There can be little doubt from the present data that the serum triglyceride concentration is more closely associated with coronary heart disease than is the serum cholesterol concentration. Using the same criterion for normality that was used for establishing a critical concentration of triglycerides, that is, the concentration found in normal young men twenty to twenty-nine years old, 260 mg. per cent is the serum cholesterol concentration best separating the normal from the abnormal. Half or more of the patients with coronary artery disease remain unidentified by this cholesterol concentration despite the clearly defined group trend (Fig. 4) for higher cholesterols in the group with coronary disease. The serum cholesterol offers its best differentiation between normal subjects and those with coronary disease in those under the age of fifty. Serum triglyceride levels provide differentiation between these groups at least equal to that of serum cholesterol for ages up to fifty, and considerably better than cholesterol over age fifty when the peak incidence of coronary occlusion occurs. The Framingham prospective study revealed data entirely comparable to those cited here with regard to the serum cholesterol concentration [*16*]. The data were not presented in such a way as to permit the evaluation of age within the group studied, but other groups [*13,31*] have found, as in the present study, that the serum cholesterol is higher in patients with coronary artery disease under fifty than in older patients.

A high concentration of serum cholesterol does, in a few instances, appear to increase the risk of coronary disease in younger age groups, even in the presence of normal serum triglycerides. A high serum cholesterol without high serum triglycerides occurred in 15 per cent of the population with coronary disease in the forty to forty-nine age bracket, but virtually did not occur after that age, although elevation of the serum cholesterol alone occurred in the normal population at a rather constant rate of about 10 per cent at all ages over thirty. (Table III.) The conclusion seems justifiable that serum cholesterol concentrations above 260 mg. per cent may carry a risk of coronary disease even without increased serum triglyceride, but only up to age fifty. Possibly the disease associated with high concentrations of serum cholesterol, but normal or nearly normal triglycerides, corresponds to familial hypercholesterolemia with xanthomatosis or a "forme fruste" of this disease [*32*], accompanied by early mortality from coronary disease and early fatal extinction by death of such per-

sons from the older population with coronary disease.

After age fifty a serum cholesterol concentration above 260 mg. per cent was found in the population with coronary disease only in association with elevated serum triglycerides. The common occurrence of high serum cholesterol *and* high triglycerides or of high serum triglycerides alone in the older patients with coronary artery disease may indicate that this abnormality is less lethal than hypercholesterolemia alone, but this latter is an infrequent or exceptional occurrence.

Although abnormal serum triglycerides are more common in coronary disease than abnormal serum cholesterol, the presence of high cholesterol may add to the risk of high triglycerides. Inspection of Table III reveals that at all ages the serum cholesterol is increased in somewhat less than half of the normal persons with high serum triglycerides, but in well over half of the patients with coronary artery disease and high triglycerides, at least through age fifty-nine.

Hypertension. Hypertension is recognized as a correlate of coronary artery disease [*16*]. Hypertension was present in 16 per cent of 250 men over age thirty, and in 29 per cent of patients with coronary artery disease, thus being twice as common in the latter group. In both normal men and patients the peak incidence of hypertension was in the sixties. The serum lipids of the hypertensive normal persons were only slightly if at all higher than the lipids of the normotensive normal men, and there were no apparent differences between the lipids of patients with and without hypertension. (Tables IV and V.) Thus the association, if any, between hypertension and elevation of serum lipids is of minor degree. The fact that hypertension without increased concentration of serum cholesterol or triglycerides was common in the normal group but almost non-existent in the group with coronary artery disease suggests that hypertension increases the risk of coronary artery disease only if associated with high concentrations of serum triglycerides, cholesterol, or both.

Significance of Other Lipid Parameters. It is well established that the three main lipid components of serum, cholesterol, phospholipids and triglycerides, are transported for the most part in lipoprotein molecules, each class of lipoprotein containing all three lipids and protein in different but characteristic relationships. The three chief categories of lipoproteins are the high density alpha lipoproteins, relatively rich in phospholipids and protein; low density beta lipoproteins in which cholesterol predominates corresponding to Gofman's S_f classes; and chylomicrons, fat particles of very low density consisting chiefly of triglyceride, appearing after a fat meal but becoming scarce in normal post-absorptive serum samples [*33,34*]. Chylomicrons are the main transport form of dietary triglycerides and impart turbidity to serum when present in substantial amounts. Abnormal lipoproteins of very low density, representing intermediate compounds between chylomicrons and beta lipoproteins, as well as chylomicrons themselves, are present in increased concentrations in the serum of patients with coronary artery disease. Lipoproteins of the class S_f 12-20 were first reported by Gofman et al. [*35*] to indicate proneness to coronary disease. Later, more emphasis was placed on the lower density class, S_f 20-100 and 100-400 [*36*].

A comparison of the present results with those reported by other workers using different lipid criteria presents some difficulties. Because of the marked skewing of the distributions, the usual comparison of means and standard deviations can have little meaning. A comparison based on the per cent of the normal population and the population with coronary disease possessing serum lipids which exceed certain arbitrary limits may be more helpful. Such a percentile comparison of the various lipoprotein parameters studied by other groups appears in Table VI. The concentration of each serum lipid or lipoprotein fraction which was exceeded by 80 per cent of the population with coronary disease was ascertained from each author's raw data and recorded in the "criterion" column. The per cent of the normal population of the same age whose lipid fraction concentration exceeded this figure was then observed, also from the raw data, and recorded in the last column. The present data also are so treated. Except in the forties, the serum triglyceride concentration exceeded by 80 per cent of the patients in each decade implicated about 30 per cent of the normal men. The other criteria listed include serum beta lipoprotein cholesterol [*37*], ratio of alpha to total lipoprotein [*38*], per cent total cholesterol in fraction A [*39*], various categories of lipoproteins and atherogenic index [*36,40*]. In the case of most other measures, in order to identify 80 per cent of the patients with coronary artery disease it was necessary to implicate over half of the

TABLE VI

OCCURRENCE IN NORMAL MEN OF SERUM LIPID ATTRIBUTES CHARACTERISTIC OF CORONARY DISEASE (THE CONCENTRATION OF EACH ATTRIBUTE WHICH IDENTIFIES 80 PER CENT OF MEN OF A GIVEN AGE WITH CORONARY DISEASE IS SHOWN IN THE THIRD COLUMN, AND THE PER CENT OF NORMAL MEN IN THE SAME AGE GROUP ALSO EXHIBITING THE ATTRIBUTE IN QUESTION IS SHOWN IN THE LAST COLUMN)

Author	Age (yr.)	Criterion Characteristic of 80 % of Coronaries	% of Normal Men Exhibiting the Criterion
Present study	30–39	Triglycerides more than 4.9 mEq./L.	33
	40–49	Triglycerides more than 3.7 mEq./L.	63
	50–59	Triglycerides more than 6.1 mEq./L.	28
	60–69	Triglycerides more than 5.6 mEq./L.	30
Present study	30–39	Total cholesterol more than 218 mg. %	47
	40–49	Total cholesterol more than 215 mg. %	63
	50–59	Total cholesterol more than 218 mg. %	68
	60–69	Total cholesterol more than 203 mg. %	73
Doyle et al. [*37*]	40–55*	Total cholesterol more than 250 mg. %	35
	40–55*	Serum beta lipoprotein cholesterol more than 200 mg. %	45
Jencks et al. [*38*]	Mostly over 45	Ratio of alpha to total lipoprotein less than 22.8	60
Barr et al. [*39*]	45–65	Cholesterol in fraction A less than 20 %	57
Jones et al. [*40*]	41–50	Total cholesterol more than 240 mg. %	47
	51–60	Total cholesterol more than 230 mg. %	70
	41–60	S_f 12-20 more than 50 mg. %	35
Technical group [*36*]	40–59	Total cholesterol more than 220 mg. %	68
	40–59	S_f 12-20 more than 34 mg. %	70
	40–59	S_f 20-100 more than 57 mg. %	65
	40–59	Atherogenic index more than 74	47

* Four persons were outside this age range.

normal population. Exceptions were the serum cholesterol and serum beta lipoprotein cholesterol reported by Doyle et al. [*37*], possibly because their population was weighted with men aged forty to fifty, in whom the serum cholesterol level does appear to be of some importance. Another exception was the lipoprotein fraction S_f 12-20 reported by Jones et al. [*40*] to show less overlap between the population with coronary artery disease and the normal population. However, judging from the data reported by the technical group [*36*], in order to identify 80 per cent of the patients with coronary disease, the critical concentration of S_f 12-20 lipoproteins would have to be lowered to 34 mg. per cent, a concentration which would implicate 70 per cent of their normal population. In this study the atherogenic index, a criterion based on several lipoproteins, particularly the low density S_f 100-400 group, provided a better basis for discrimination than the S_f 0-12 or 12-100 alone. Data reported by Lawry et al. [*13*] indicate that the two most studied lipoprotein categories, S_f 12-20 and 20-100, like the serum cholesterol, permit discrimination only up to about age fifty, failing to show differences between normal persons and those with coronary artery disease after that age.

An abnormally high concentration of low density and very low density lipoproteins may reflect and indeed be attributed to an increasing concentration of serum triglycerides. That triglycerides are an increasingly prominent constituent of lipoproteins of increasingly lower density has been appreciated [*33,41*]. Recently a predictable relationship between triglyceride concentration and the presence of low density lipoproteins was demonstrated: in postabsorptive serum samples the relationship between triglyceride concentration and lipoprotein density was sufficiently close to permit estimation of the relative concentrations of the various low density lipoproteins from the total concentrations of the serum cholesterol and triglycerides [*21*]. The presence in serum of triglycerides in concentrations greater than 6 mEq./L. was associated with

a shift of cholesterol into lipoproteins of very low density, a shift which became increasingly marked with each progressive rise in concentration of triglycerides. The triglyceride concentration at which these changes begin to occur is notably close to the concentration separating the normal from the coronary groups in the present study. Lindgren and Gofman found, similarly, that the atherogenic index could be estimated from a combination of serum total cholesterol and total lipid, a relationship probably dependent on the fact that except in instances of "pure" hypercholesterolemia, triglycerides become an increasingly prominent constituent of plasma as the total lipids increase.

There is growing awareness that measurement of the very low density classes S_f 100-400 might be more revealing than the customarily measured fractions S_f 12-20 and 20-100 [*42*]. Schlesinger et al. [*43*] found that the sum of all low density lipoproteins S_f 1-400 correlated better with coronary disease than any one class, and as well as the weighted atherogenic index. The concentration of serum triglycerides gives, in a sense, an already weighted summation not only of lipoproteins S_f 1-400, but also of all the low density fractions including those of S_f 400 and greater, which become more prominent as the total triglycerides increase. As an added advantage, the serum triglycerides can be measured in most laboratories without special equipment, in contrast to lipoprotein density determinations.

Intensified and prolonged alimentary lipemia occurs in patients with coronary artery disease [*5*], and has been considered an indication of impaired ability to remove triglycerides from the blood stream. All the serum samples in the present study were measured in the fasting state. The measurement of alimentary lipemia seems more cumbersome and more subject to the variables of intestinal absorption. Low density lipoproteins S_f 20 or less are said not to be influenced by the immediate past ingestion of fat [*35*], but the very low density lipoproteins, which may be of importance in coronary artery disease, might be so influenced. The present plan is to continue to study serum lipids obtained from persons in the postabsorptive state.

The factors determining the postabsorptive concentration of serum triglycerides are largely unknown. The concentration may be markedly increased in diabetic acidosis (only rarely in controlled diabetes) [*44–46*], nephrosis [*47*], acute pancreatitis [*48*], acute ingestion of alcohol [*49*] and, in some instances, after starvation for several days [*50,51*]. Such hormones as epinephrine [*52*], growth hormone [*53*] and cortisone [*54*] may also cause a temporary rise in serum triglycerides in man and in experimental animals. Stimulation of carbohydrate metabolism lowers the serum values [*55,56*]. A high carbohydrate, low fat diet may increase the postabsorptive serum triglyceride concentration [*57–59*] although South African natives and white prison inmates receiving low protein, high carbohydrate diets do not show such elevation [*4*]. The importance of considering the serum triglyceride concentration in the therapy of coronary artery disease is manifest by the differing response of various types of hyperlipemias to different dietary treatments of this disease [*60*]. Cholesterol and triglyceride levels in the blood may change in opposite direction following administration of certain drugs [*61*].

A causal relationship of serum lipids to coronary artery disease is unproved. The similarity between lipids of serum and of atheromatous deposits has led to the hypothesis that atheromas arise from deposition of serum lipids, particularly cholesterol, in the subendothelial space. Even if the plaque lipids originate from serum, the concentration of serum lipids is unlikely to be the sole determinant of atheroma formation. The serum cholesterol concentration during life has little relation to the degree of atherosclerosis at death [*62*]. The relationship of serum triglycerides to atheroma formation is as yet unknown, although the possibility that triglycerides may have special significance in coronary artery disease is suggested by the finding that coronary atheromas have a higher triglyceride content than do atheromas of the aorta, where proportionately more cholesterol has been found [*63*]. The possible importance of serum triglycerides in atheroma formation is further supported by Waters' finding that triglyceride-rich lipoproteins of very low density, when injected into the rabbit cornea, an avascular connective tissue similar to aorta, caused pathologic changes similar to arteriosclerotic changes in man [*64*].

Many workers are opposed to the theory that atheroma lipids are derived from the lipids of serum [*65*]. Zilversmit reports that phospholipids and possibly other lipids of atherosclerotic plaques are synthesized, not deposited, in the

arterial wall [*66*]. Alternatively, serum lipid abnormalities could be merely a coincidental by-product of an enzymatic disorder on a cellular level, a biochemical defect which is the cause rather than the result of the increased concentration of serum lipids. Such a generalized inability to metabolize fat might be particularly detrimental to the myocardium. The importance of fat as fuel for the heart is suggested by the known ability of heart muscle to metabolize fat [*67*], by the important extent to which normal myocardium subsists on fat in the fasting state [*68*], and by the rich stores of lipoprotein lipase present in myocardial tissue [*33*].

Coronary artery disease appears to have many causes, and defective triglyceride metabolism may be merely a part of a more complex metabolic abnormality characterized by altered ability to metabolize fat, and manifested by coronary atheromas in parallel with elevation of the serum triglycerides. Whatever theories ultimately prove to be correct, the serum triglycerides appear to fulfill, better than do other lipid indicators, the criteria for a serum diagnostic factor in coronary artery disease.

SUMMARY

The serum lipids were measured in 115 patients who had suffered a myocardial infarction at least ten days previously and in 397 apparently healthy men of various ages. All persons studied were in the postabsorptive state. A smaller number of normal women and women who had suffered a coronary attack was also investigated. A few persons with diabetes were considered separately.

Serum triglyceride concentrations were increased above 5.4 mEq./L. in 5 per cent of seventy-three normal men twenty to twenty-nine years of age, in 36 per cent of 325 normal men aged thirty and over, and in 82 per cent of all patients with coronary artery disease. High serum cholesterol concentrations or hypertension appeared to increase the risk of coronary disease in persons with high serum triglycerides, but by themselves seemed to carry little risk. An exception was the occurrence of high serum cholesterol without high serum triglycerides in a small number of patients with coronary artery disease under age fifty. At all ages, however, the vast majority of patients exhibited an increase in serum triglyceride concentration as the most characteristic abnormality.

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Hypercholesteremia and Nicotinic Acid

A Long-Term Study

KENNETH G. BERGE, M.D., RICHARD W. P. ACHOR, M.D., NORMAN A. CHRISTENSEN, M.D., HAROLD L. MASON, PH.D. *and* NELSON W. BARKER, M.D.

Rochester, Minnesota

As there is experimental and clinical evidence that hypercholesteremia is at least one important factor in atherogenesis, many regimens of diet and medication have been designed to lower elevated levels of lipids in the blood of man. To date, all such programs of treatment have had handicaps such as lack of uniform effectiveness, impracticality, prohibitive expense, excessive side effects or toxic reactions. In 1955, following the report by Altschul and co-workers [*1*] that large oral doses of nicotinic acid decreased the concentration of plasma cholesterol in a short term study of human subjects, a long term study of such treatment was undertaken. A rather voluminous and somewhat contradictory literature regarding the effectiveness, mechanism of action and side effects of large doses of nicotinic acid has subsequently appeared. Therefore, it seems worth while to report in detail our total experience with this treatment, which includes sixty-six persons, six of whom have been under continuous observation for more than four and a half years.

TABLE 1
TREATMENT OF HYPERCHOLESTEREMIA WITH NICOTINIC ACID

Duration of Treatment	Patients
Less than one year	15
Stopped treatment because of side effects	8
Moved away and could not be followed up	2
Died during first year of treatment	2
Began treatment less than one year previously	3
One year or more	51
At least two years	19
At least three years	13
At least four years	6

METHODS

Persons were selected for study if the fasting level of cholesterol in their plasma exceeded 250 mg. per 100 ml. and if circumstances of residence or travel permitted visits to the clinic at least monthly for blood tests and clinical observation. The majority of the group resided in Rochester, Minnesota. None had hypothyroidism or nephrosis. All persons selected were followed up as outpatients, except during intercurrent illnesses, and were advised to continue the same diet and program of other medications used prior to entering the study. Complete physical examinations and appropriate laboratory tests were performed prior to and at yearly intervals during the course of the study. The laboratory studies included routine urinalysis, determinations of hemoglobin and leukocytes, tests of hepatic function and carbohydrate tolerance, determinations of blood urea, roentgenographic examination of the thorax, and twelve lead electrocardiographic examination. Careful notations were made of observations on symptoms or signs of coronary and peripheral arterial insufficiency and of the size of cutaneous or tendinous xanthomas.

Nicotinic acid was administered in the form of a capsule or tablet containing 0.5 gm.† The initial dosage was 3 gm. daily taken in three divided doses with meals. Dosage was changed at intervals of no less than three months so that the effect of a given dosage might be studied for a significant period. The largest daily amount used was 6 gm. After six or nine months of treatment with nicotinic acid, a placebo capsule or tablet was administered for three months.

Samples of venous blood for determination of lipids were drawn in the fasting state in the regular clinical laboratory before institution of treatment with nicotinic acid, at intervals of two or four weeks during the first year of study, and every month subsequently. Plasma cholesterol was determined by the method of Bloor [*2*] prior to November 1957, when the method of Zak [*3*] was substituted. During the first year of treat-

† Kindly supplied by Eli Lilly and Company, Indianapolis, Indiana.

* From the Departments of Medicine and Biochemistry, the Mayo Clinic and the Mayo Foundation, Rochester, Minnesota. The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

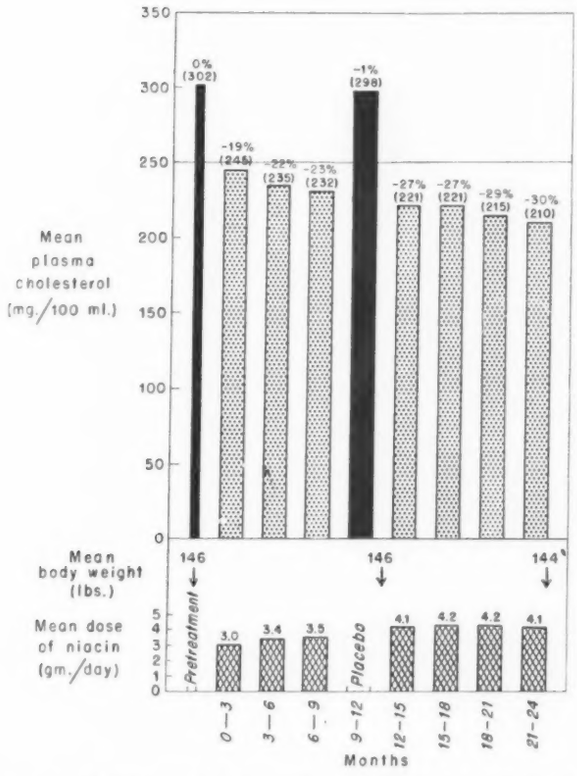

FIG. 1. Mean levels of plasma cholesterol, body weight and dosage of nicotinic acid in nineteen persons treated for two years.

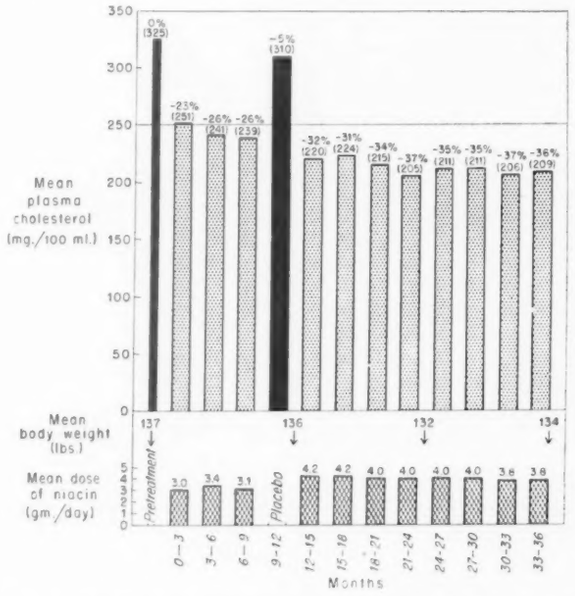

FIG. 2. Mean levels of plasma cholesterol, body weight and dosage of nicotinic acid in thirteen persons treated for three years.

ment for each patient, plasma phospholipids were determined by the Maclay modification of the Gomori method [*4*], and total lipids by the method of Bloor [*5*]. The cholesterol in the various fractions of serum lipoprotein was determined electrophoretically in sixteen persons during the first year of study [*6*].

RESULTS

Prior to March 1960, sixty-six persons had begun the program of study just described and fifty-one had participated for at least one year. Data concerning the periods of study are presented in Table I. The side effects, which necessitated discontinuing the use of nicotinic acid in eight instances, will be commented upon later in this report. Thirty-nine patients followed an unrestricted diet, twenty-three adhered to a diet moderately to minimally restricted in fat content, two had diets prescribed for reduction of weight, and two followed diets for duodenal ulcer. Data on body weight (Figs. 1, 2 and 3) and the comparison of concentrations of lipids before treatment and during the period of placebo administration suggest that there were no significant alterations in diet during the study. The response to nicotinic acid was not assessed according to the diet followed.

Plasma Lipids. The mean changes in the plasma concentration of cholesterol, phospholipid and fatty acids in the fifty-one persons treated for at least one year are presented in Table II. The mean decrease in cholesterol of 19 per cent from the mean pretreatment level of 327 mg. per 100 ml. during the first three months was highly significant statistically ($P = < .001$). A further mean decrease of 4 per cent when the mean daily dosage of nicotinic acid was increased by 0.7 gm. during the second three months was also significant ($P = < .01$). The mean level of phospholipid decreased during treatment, but to a lesser degree than did that of cholesterol, so that the cholesterol : phospholipid (C : P) ratio was decreased to more nearly the normal level of 1:0 or less. The changes in concentration of fatty acids paralleled those of cholesterol but were of somewhat lesser magnitude. The rise in level of plasma cholesterol when the placebo was substituted for nicotinic acid was highly significant ($P = < .001$).

The results for the same fifty-one persons are given in Table III according to percentage change in the concentration of plasma cholesterol from the individual pretreatment level. It is apparent that as the dosage of nicotinic acid was increased, a greater number of persons exhibited a greater

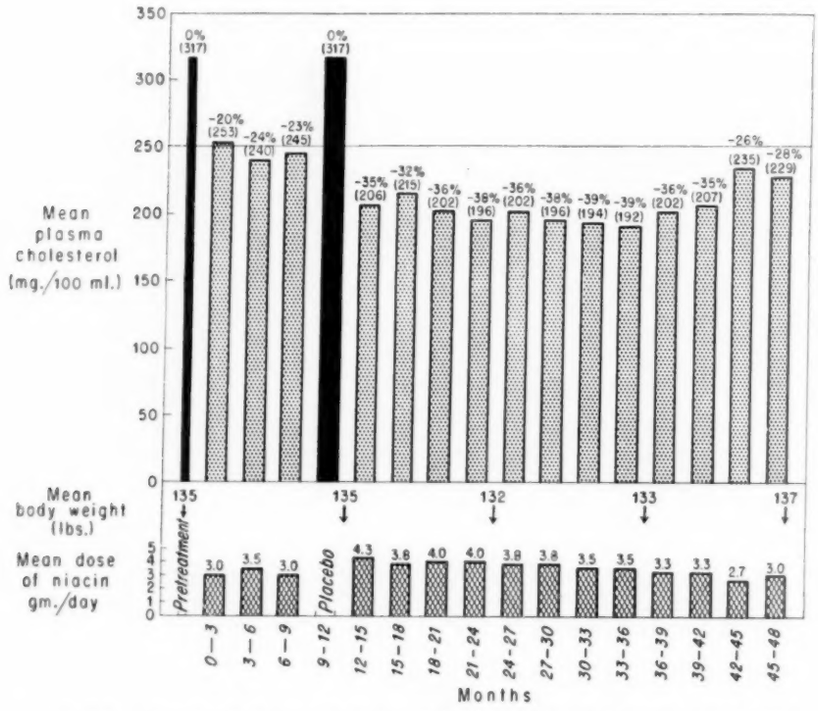

FIG. 3. Mean levels of plasma cholesterol, body weight and dosage of nicotinic acid in six persons treated for four years.

decrease in the concentration of cholesterol. The significance of this direct relationship between dosage and response, also evident in Table II, was studied further in thirty persons who received two different dosages for three months each. (Table IV.) The further decrease in the level of plasma cholesterol when the daily dose of nicotinic acid was changed from 3 to 4.5 gm. is highly significant statistically ($P = < .001$). Our experience with larger doses (6 gm. daily) is not extensive enough to permit statistical analysis, although in certain persons this larger dose did produce a further decrease in the level of plasma cholesterol. Parsons and Flinn [7] reported that doses in the range of 7.5 to 9 gm. daily did not improve further the results noted with doses of 4.5 or 6 gm.

The values for plasma cholesterol were also

TABLE II

CHANGES IN BLOOD LIPIDS DURING TREATMENT WITH NICOTINIC ACID ON THE BASIS OF FIFTY-ONE PERSONS TREATED FOR ONE YEAR

Period	Mean Determinations per Person	Nicotinic Acid* (gm./day)	Plasma Cholesterol				Phospholipid		C:P Ratio‖		Fatty Acids	
			mg./100 ml.		P Value‡	Per cent Change§	mg./100 ml. (mean)	Per cent Change§	Ratio	Per cent Change§	mg./100 ml. (mean)	Per cent Change§
			Mean	S.E.†								
Pretreatment	2.4	...	326.8	±7.2	...	0	289.8	0	1.13	0	523.0	0
0 to 3 months	5.9	3.0	266.3	±7.1	<0.001	−19	259.0	−11	1.03	−8	449.5	−14
3 to 6 months	5.3	3.7	251.0	±6.9	<0.01	−23	248.0	−14	1.01	−10	430.2	−18
6 to 9 months	5.0	3.9	250.0	±8.3	<0.9	−24	249.0	−14	1.00	−11	420.6	−20
9 to 12 months	5.0	Placebos	305.7	±8.1	<0.001	−7	283.7	−2	1.08	−4	508.5	−3

* Mean.
† Standard error.
‡ Value less than 0.05 indicates significant change from value in preceding period.
§ Change from pretreatment level.
‖ Cholesterol: phospholipid ratio.

TABLE III

PERCENTAGE CHANGE IN CONCENTRATION OF PLASMA CHOLESTEROL DURING TREATMENT WITH NICOTINIC ACID, ON THE BASIS OF FIFTY-ONE PERSONS TREATED FOR ONE YEAR

Percentage Change from Individual Pretreatment Levels of Plasma Cholesterol	Number of Persons			
	Zero to Three Months (3.0 gm./day)*	Three to Six Months (3.7 gm./day)*	Six to Nine Months (3.9 gm./day)*	Nine to Twelve Months (placebo)
+10 to +20	...	...	1	5
0 to +9	4	1	1	9
−1 to −9	6	6	7	15
−10 to −19	19	11	8	18
−20 to −29	15	19	18	4
−30 to −39	5	11	11	...
−40 to −49	1	3	5	...
−50 to −59	1	...	...	...
Total	51	51	51	51

* Mean dose of nicotinic acid.

TABLE IV

NICOTINIC ACID AND HYPERCHOLESTEREMIA: RELATIONSHIP OF DOSE TO RESPONSE IN THIRTY CASES

Period	Nicotinic Acid (gm./day)	Plasma Cholesterol		
		mg./100 ml.* (mean)	P Value†	Per cent Change‡
Pretreatment	...	332.6 ± 9.7	...	...
0 to 3 months	3.0	283.3 ± 7.5	<0.001	−15
3 to 6 months	4.5	249.4 ± 8.7	<0.001	−25

* Number following ± is standard error.

† Values less than 0.05 indicates significant change from value in preceding period.

‡ Change from pretreatment level.

tabulated for the three month period in which each of the fifty-one persons exhibited his best response to nicotinic acid therapy during the first year of study. Forty-one persons (80 per cent) achieved a mean cholesterol level of less than 250 mg. per 100 ml. during this three month period. The mean concentration of plasma cholesterol for this group of forty-one persons was 201 mg. per 100 ml. while they were taking a mean dose of 4.1 gm. of nicotinic acid daily, a decrease of 36 per cent from their mean pretreatment level (314 mg. per 100 ml.). The ten persons (20 per cent) whose mean cholesterol level was still greater than 250 mg. per 100 ml. during the three month period of best response had a higher mean pretreatment level (382 mg. per 100 ml.) than did the aforementioned group, and it decreased less (to 309 mg. per 100 ml.; 19 per cent) in spite of a larger daily dose of nicotinic acid (4.7 gm.). Factors associated with poorer response will be considered later in this report.

Following completion of the first year of study, ten persons whose hypercholesteremia was relatively refractory to treatment with nicotinic acid were given other medications [*8*]. This accounts, in part at least, for the better mean response of these persons studied for two, three and four years as compared with the response noted for the first year in the entire group. (Figs. 1, 2 and 3.) The data for the longer periods of treatment indicate a well sustained effect and a continued relationship of response to the dosage of nicotinic acid used. There did not appear to be any "escape" from the effectiveness of treatment over long periods; if anything, a better response was observed later with the same dosage as that used initially. The lack of any significant change in body weight is apparent (Figs. 1, 2 and 3) in these long-term patients who tolerated therapy well.

The response of plasma cholesterol to nicotinic acid during the initial three months of treatment of fifty-nine persons was assessed with respect to age and sex, pretreatment level of cholesterol, and diagnosis. (Table v.) Except in the small category of four persons with cerebrovascular disease, the responses were similar in the various diagnostic categories. Furthermore, the percentage decrease in plasma cholesterol in the group of twenty-one persons whose pretreatment level exceeded the mean of 332 mg. per 100 ml. was not significantly different from that in the group of 38 persons whose level was lower than this mean. These data, based on a larger number of cases, do not bear out our earlier impressions [*6*] or those reported by Parsons and Flinn [*7*] that persons with xanthoma tuberosum or xanthoma tendinosum and those with lower initial levels of plasma cholesterol are less responsive to treatment. Women, both those older and those younger than the mean age of forty-seven years, had a better response than did the men. As a group, the younger men had the poorest response (minus 14 per cent).

The effects of nicotinic acid on the concentration of beta-lipoprotein cholesterol in the plasma of the sixteen persons so studied paralleled

TABLE V
EFFECT OF NICOTINIC ACID ON HYPERCHOLESTEREMIA (RESPONSE DURING FIRST THREE MONTHS OF TREATMENT IN FIFTY-NINE PATIENTS)

Data	Patients		Plasma Cholesterol		
			mg./100 ml. (mean)		Per cent Decrease
	Number	Per cent	Before Treatment	Treatment for Three Months*	
Sex					
Male	43	73	330	279	−15
Female	16	27	338	262	−22
Total	59	100	332	274	−17
Age (range 7 to 66 years of age; mean 47)					
47 or older					
Females	11	19	346	266	−23
Males	19	32	331	276	−17
Total	30	51	336	272	−19
46 or younger					
Females	5	8	322	252	−22
Males	24	41	329	282	−14
Total	29	49	328	277	−16
Pretreatment cholesterol					
More than 332 mg./100 ml.	21	36	400	330	−18
Less than 332 mg./100 ml.	38	64	295	244	−17
Diagnosis					
Disease of coronary arteries	33	56	339	284	−16
Known familial hypercholesteremia	24	41	364	303	−17
Xanthoma tendinosum	15	25	395	337	−15
Arterial hypertension	10	17	312	261	−16
Arteriosclerosis obliterans	11	19	342	292	−15
Cerebrovascular disease	4	7	302	276	−9

* With 3 gm. per day.

closely the change in total plasma cholesterol, as reported previously [*9*].

Effect of Treatment on Xanthomatous Lesions. In one of fifteen persons with xanthoma tendinosum, xanthomas of the extensor tendons of the fingers disappeared and in another patient the size of the lesions decreased definitely during treatment with nicotinic acid. Cutaneous xanthomas of the olecranon area in another patient decreased in size during such treatment, which extended over three years. (Fig. 4.) Xanthelasmas of the eyelids disappeared in one person and decreased in size in two others.

Course of Coronary Arterial Disease. Thirty-three of the sixty-six persons studied had clinical evidence of disease of the coronary arteries at the time of entering the study. Angina pectoris, present in twenty-nine persons, became subjectively worse in two, was unchanged in fifteen and became less evident in twelve during the periods of treatment with nicotinic acid. Exercise tolerance tests were not performed in persons with clinically evident coronary disease. We are reluctant to ascribe any significance to subjective improvement in patients participating in a study such as this. Furthermore, acute myocardial infarction or sudden cardiac death occurred in four patients during treatment and in eight other persons during the period of placebo administration or after leaving the study. The only person who sustained two acute myocardial infarctions during treatment with nicotinic acid had noted disappearance of tendinous xanthomas earlier in the course of three years of treatment, during which time a very satisfactory reduction in the level of plasma cholesterol was maintained. These results emphasize that the course of coronary atherosclerosis or its complications may not necessarily parallel improvement in lipid levels in the plasma or changes in lipid deposits elsewhere in the body [*10*].

Twelve (18 per cent) of the sixty-six patients beginning the study have died, and necropsy was performed in nine. Death was due to coronary disease in ten patients and to combined coronary and cerebrovascular disease in one other. Three of these persons died during treatment with nicotinic acid; two during the three months a placebo was administered, four after treatment with nicotinic acid was stopped (four and a half months, six months, eight months and one year later, respectively), and two while receiving other hypocholesteremic drugs or placebos. One additional patient died of fulminating hepatitis seven months after nicotinic acid therapy had been discontinued and while he was taking an estrogenic medication for hypercholesteremia. There was no way to assess pathologically what effect, if any, prior treatment had exerted on the atherosclerotic lesions of the persons examined at necropsy.

Effects of Treatment on Arteriosclerosis Obliterans. Intermittent claudication was noted prior to treatment by ten persons. During treatment with nicotinic acid, this symptom was worse in one, unchanged in five and less evident in four. In two of the last group, determinations of the claudication time made before and during treatment indicated modest improvement. The ability to walk at a set pace was increased from five to eight minutes in one person and from fifteen to eighteen minutes in another during treatment with nicotinic acid. No significant

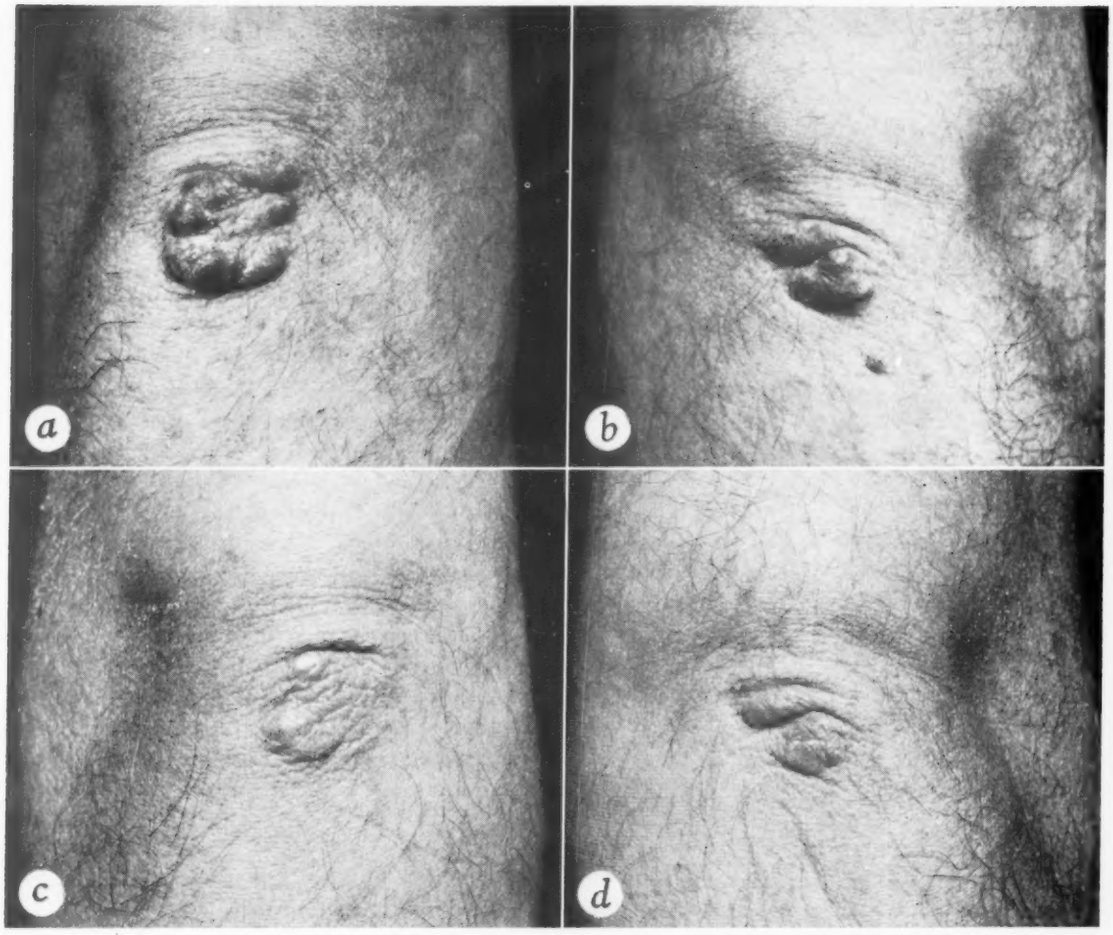

FIG. 4. Xanthoma tuberosum of both elbows in a forty year old man with idiopathic hypercholesteremia before (a) and (b) and after (c) and (d) treatment with nicotinic acid for twenty-seven months. Pretreatment and placebo levels of plasma cholesterol were 294 and 307 mg. per 100 ml., respectively; the mean level during treatment was 231 mg.

improvement in arterial pulsations of the lower extremities was noted in any of the ten patients.

Side Effects. Data on symptoms occurring during treatment with nicotinic acid are given in Table VI. Cutaneous flushing, noted to some extent by all persons initially, was of moderate or severe degree in only 13 per cent of the persons after the initial two weeks of treatment. Pruritus and mild urticaria occasionally occurred with the more severe flushing. A chronic history of flushing of mild degree, especially with the first daily dose of nicotinic acid, could be obtained from 59 per cent of patients after the initial period of treatment but was not an objectionable side effect.

Although dryness of the skin was apparent and was associated with pruritus in several instances, no definite dermatologic abnormalities were noted. Parsons and Flinn [7] have reported the occurrence of a rash resembling acanthosis nigricans in two cases, and Ruiter and Meyler [11] have reported pigmentary disturbances and lesions suggesting ichthyosis vulgaris in one case during treatment with large doses of nicotinic acid. One of our patients reported an increase in furunculosis during treatment.

Gastrointestinal irritation with anorexia, nausea, vomiting or diarrhea was noticed by 20 per cent of the patients during the first two weeks of treatment, and by 28 per cent over longer periods. Usually these symptoms were mild or transitory, but four persons discontinued treatment because of them. In one person, esophagitis developed as a complication of an esophageal hiatal hernia during treatment, but the symptoms cleared after the dosage of nicotinic acid was decreased. In no instance was the production of peptic ulceration noted, and the

TABLE VI
SYMPTOMS OCCURRING DURING NICOTINIC ACID THERAPY

Symptom	Initial Period, One to Fourteen Days (sixty-six patients)				Late Effects (sixty-one patients)	
			Duration (days)			
	Patients	Per cent	One to Three	Four to Four-teen	Patients	Per cent
Cutaneous flushing, burning and pruritus						
Severe	45*	68	27	18	2	3
Moderate	16	24	11	5	6*	10
Mild	5	8	5	0	36	59
None	0	0	0	0	17	28
Anorexia, nausea or vomiting, or combinations thereof	13†	20	...	...	11‡	18

* Two patients withdrew from study because of symptoms.
† Four patients withdrew from study because of symptoms.
‡ One patient had transient esophagitis complicating an esophageal hiatal hernia. In two instances dosage was decreased because of symptoms.

two persons with previously known duodenal ulcer experienced no exacerbation of symptoms during therapy with nicotinic acid. Ingestion of the nicotinic acid with meals appeared to diminish the gastrointestinal reaction as well as the cutaneous flushing.

Tests of Hepatic Function. Tests of hepatic function, including determinations of sulfobromophthalein retention, serum bilirubin, cephalin-cholesterol flocculation, alkaline phosphatase activity and serum glutamic-oxalacetic transaminase activity, were carried out periodically. In twenty-seven patients all of these tests gave normal results. In two others, only the determination of sulfobromophthalein retention and of serum bilirubin were performed and gave normal results. Tests were made during treatment in twenty-six of these patients and at the end of the placebo period in three others.

Twenty-three patients exhibited at least one abnormal result in a test of hepatic function, that is, retention of more than 6 per cent of sulfobromophthalein in one hour, the presence of more than 0.0 mg. of direct and 1.0 mg. indirect serum bilirubin per 100 ml., grade 3 or 4 cephalin-cholesterol flocculation, more than 16 King-Armstrong units of alkaline phosphatase, and transamination of more than 1.43 μM per ml. per hour for serum glutamic-oxalacetic transaminase activity. In twelve patients the abnormal results returned to normal; in five this occurred without change in the dosage of nicotinic acid, in two when the dosage was decreased, and in five when use of the drug was stopped or the placebo substituted. In three persons abnormal results were observed only during the period of placebo administration or after treatment had been discontinued, and these results were associated with alcoholism in two of the three. In five other patients abnormal results obtained with the sulfobromophthalein test (three), the cephalin-cholesterol flocculation test (one), or the test for serum glutamic-oxalacetic transaminase activity (one) have not been rechecked. In only three patients has a test or tests given persistently abnormal results (cephalin-cholesterol flocculation in one; sulfobromophthalein retention and cephalin-cholesterol flocculation in the second; and sulfobromophthalein retention, cephalin-cholesterol flocculation and alkaline phosphatase in the third), but treatment has been continued. Retention of sulfobromophthalein, noted in ten patients, was of grade 1 in six, grade 2 in three, and grade 3 in one.* The four persons in the last two groups had no retention when follow-up tests were made.

Jaundice. Jaundice has occurred in two cases during treatment with nicotinic acid. In neither case was there a history of exposure to persons with known hepatitis or of contact with hepatotoxins prior to development of the jaundice. In both cases the increased concentration of serum bilirubin, which was mainly of the direct-reacting type, promptly returned to normal levels during observation following withdrawal of nicotinic acid. Needle biopsy during the period of jaundice in one of the two cases disclosed a histologic picture similar to that seen with viral hepatitis, including acidophilic necrosis of hepatic cells and minimal leukocytic infiltration. Both patients were receiving sustained-release type of preparations of nicotinic acid prior to the onset of icterus. Details of these cases and experience with such preparations of nicotinic acid will be presented in a subsequent communication.

Studies of hepatic tissue were made at necropsy in nine cases. Mild fatty change was noted in two cases in which death occurred during treatment with nicotinic acid. In addition, small focal

* Grade 1 indicates between 6 and 10 per cent retention in 1 hour; grade 2, 12 to 22 per cent; and grade 3, 24 to 38 per cent.

areas of necrosis were noted in one and passive congestion in the other. In the other seven cases, necropsy was performed five weeks to one year after treatment with nicotinic acid. Fatty changes were graded as mild in five, moderate in one, and absent in one. One person in this group, who died five weeks after cessation of treatment with nicotinic acid, also exhibited focal necrosis of hepatic cells.

Abnormal results in tests of hepatic function during treatment with large doses of nicotinic acid have been reported from this institution previously [*12,13*]. Parsons and Flinn [*7*] noted no abnormal results either in tests of hepatic function (sulfobromophthalein retention, serum bilirubin, cephalin-cholesterol flocculation, thymol turbidity, serum glutamic-oxalacetic transaminase activity, alkaline phosphatase, total proteins and electrophoresis of serum proteins) or needle biopsies of the liver in seventeen patients after one year of study, but they observed retention of sulfobromophthalein in six of forty-nine patients after one to three years of treatment. Rivin [*14*] has recorded the occurrence of jaundice during treatment of hypercholesteremia with nicotinic acid in one patient, but this patient did not resemble either of our two patients with jaundice in that the serum bilirubin was primarily of the indirect-reacting type.

Carbohydrate Metabolism. Fasting blood sugar, oral glucose tolerance or both were determined during treatment in thirty-one persons. One of these persons had mild diabetes mellitus prior to entering the study, and is not included in the following discussion. Pretreatment glucose tolerance tests were not performed routinely.

The present method of determining blood sugar used at the Mayo Clinic includes little if any non-glucose-reducing substances [*15*]. The current, arbitrary criteria for the evaluation of carbohydrate tolerance based on the fasting level of this "true" blood sugar (mg. per 100 ml.) are as follows: normal 65 to 90, equivocal 91 to 110, and abnormal 111 or more. Similar criteria for the levels of blood sugar during the oral glucose tolerance test are: normal, 140 or less at one hour and 90 or less at two hours; equivocal, 141 to 150 at one hour and 91 to 110 at two hours; and abnormal, more than 150 at one hour and more than 110 at two hours.

During treatment with nicotinic acid the concentration of fasting blood sugar was normal in nine persons but exceeded 90 mg. per 100 ml.

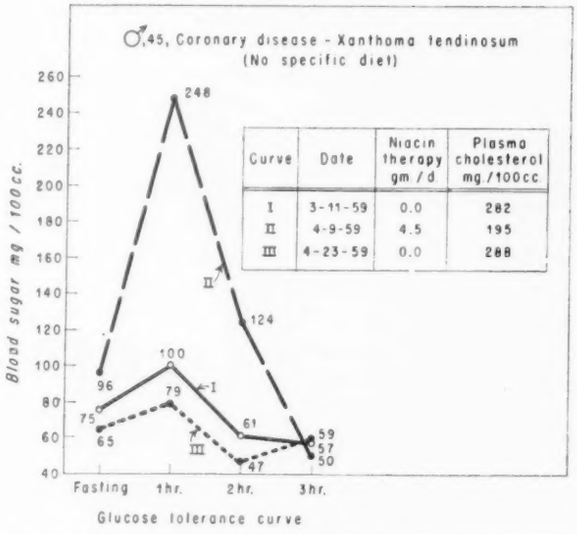
♂,45, Coronary disease - Xanthoma tendinosum
(No specific diet)
Curve | Date | Niacin therapy gm / d | Plasma cholesterol mg./100cc
I | 3-11-59 | 0.0 | 282
II | 4-9-59 | 4.5 | 195
III | 4-23-59 | 0.0 | 288
Blood sugar mg / 100cc.
Fasting
1hr.
2hr.
3hr.
Glucose tolerance curve

FIG. 5. Oral glucose-tolerance tests before, during and after treatment with nicotinic acid in dosage of 4.5 gm. daily. Note prompt return of glucose tolerance and plasma cholesterol to pretreatment levels two weeks after nicotinic acid therapy was discontinued.

in 21 (91 to 99 mg. per 100 ml. in eleven cases, 100 to 110 in eight, and more than 110 in two). The highest level observed was 171 mg. per 100 ml.

Glucose tolerance tests were performed during treatment with nicotinic acid and with adequate preliminary intake of dietary carbohydrate in twenty-seven persons. The results based on the aforementioned criteria were normal in eight persons, five of whom had had an elevated value for fasting blood sugar, equivocal in five, and abnormal in fourteen. In three persons the abnormalities of carbohydrate tolerance were not associated with fasting hyperglycemia.

The result of stopping treatment with nicotinic acid was assessed in eighteen of the nineteen persons whose glucose tolerance tests gave equivocal or abnormal results. In thirteen the results were normal after an interval without nicotinic acid (after two weeks or less in nine, three weeks in one, two months in one, and three months in two). The results in one person in this group are presented graphically in Figure 5. In three patients the results of the glucose tolerance test were still equivocal after an interval without treatment of two, three and four months, respectively. One additional person had an equivocal result just prior to a myocardial infarction causing death two and a half months after nicotinic acid therapy had been discon-

tinued. Another patient had evidence of mild diabetes mellitus six months after use of the drug was stopped; this last person was obese and had a family history of diabetes mellitus. The one person who had mild diabetes mellitus as evidenced by abnormal glucose tolerance prior to treatment had values ranging from 83 to 97 mg. per 100 ml. for fasting blood sugar during treatment with nicotinic acid and while following a diet moderately restricted in carbohydrate. No glycosuria was noted.

Clinical observations on abnormalities of carbohydrate metabolism during treatment of hypercholesteremia with large doses of nicotinic acid were reported initially by Gurian and Adlersberg [*16*], who noted hyperglycemia in five instances and glucose tolerance curves simulating those of diabetes mellitus in two. They observed that the effect of nicotinic acid on carbohydrate tolerance was observed earlier than that on serum lipids. They also treated three patients with adult-onset type of diabetes with nicotinic acid. In two patients taking insulin, no change in insulin requirements was reported. In an additional case a considerable increase of insulin dosage was noted [*17*]. Parsons and Flinn [*7*] reported no evidence of significant effect of nicotinic acid on the control of diabetes in three patients, but Parsons [*18*] subsequently reported impairment of glucose tolerance and the infrequent appearance of "frank diabetes" which was reversible when the use of nicotinic acid was discontinued.

Lammers and co-workers [*19*] have observed a hyperglycemic effect of nicotinic acid in rats. The mechanism by which large doses produce abnormalities in carbohydrate tolerance simulating diabetes mellitus is not known. Although pellagrins are hypersensitive to insulin, it has been observed that in normal persons nicotinic acid enhances the effect [*20*] of insulin. It has been stated that 500 mg. of nicotinic acid in a single dose produces hypoglycemia [*20*]. If the mechanism by which large doses of nicotinic acid alters carbohydrate metabolism is discovered, it may be possible to establish the significance of this abnormality.

Uric Acid and Gout. Hyperuricemia (uric acid, 6 mg. or more per 100 ml. of serum) was present on at least one occasion in sixteen (62 per cent) of twenty-six patients so tested during treatment with nicotinic acid. In eight of these sixteen patients, all seventeen determinations of uric acid during treatment showed increased levels with a mean level of 7.8 mg. per 100 ml. The value for uric acid in serum of six of these patients was checked on two separate occasions by the uricase method, which gave levels essentially the same as had been obtained by the routine (Folin) chemical method. In the other eight patients exhibiting hyperuricemia, one or more values were normal and the mean was 6 mg. per 100 ml. Five of this group had subsequent normal levels of uric acid without stopping treatment. Two persons experienced single episodes of acute gouty arthritis during treatment with nicotinic acid. One of these patients had had attacks of gout before beginning nicotinic acid therapy. The other patient, a fifty-three year old woman, had her first attack twenty-four months after initiation of therapy but has had no subsequent attacks although therapy has been continued without interruption for an additional twenty-one months. In five persons the hyperuricemia occurred in association with hyperglycemia. de Soldati and co-workers [*21*] reported increased concentrations of uric acid in four of nineteen persons treated with nicotinic acid, and Parsons [*18*] observed this phenomenon in 29 of 40 persons so treated. The cause of the hyperuricemia associated with the administration of nicotinic acid is not known.

COMMENTS

The data presented and those reported in the literature [*1,7–9,12,14,16,21–33*] indicate clearly that prolonged oral administration of large doses of nicotinic acid produces a significant reduction in the level of plasma cholesterol in a majority of patients with hypercholesteremia without alteration in the usual diet. This response is sustained as long as the drug is given and is related to the dosage of nicotinic acid used. The hypocholesteremic response to nicotinic acid has proved superior to that observed with the use of β-sitosterol or from the addition of unsaturated fats in the absence of other dietary changes [*8*]. The combined use of nicotinic acid and β-sitosterol is more effective than the use of either agent alone, and nicotinic acid may induce a further decrease of plasma cholesterol in persons on a diet low in saturated fats. Several studies have shown that large doses of nicotinic acid decrease the hypercholesteremia and inhibit or prevent the atheromatosis of rabbits fed cholesterol [*34–37*].

Although treatment with nicotinic acid is relatively inexpensive and practical to employ,

the occurrence of side effects continues to limit its widespread clinical application. In addition to cutaneous flushing and symptoms of gastrointestinal irritation, abnormalities of hepatic function, carbohydrate tolerance and uric acid metabolism have been associated with such treatment. Although the side effects may not contraindicate the use of large doses of nicotinic acid as an investigational procedure [*38*] in most patients with hypercholesteremia, they do indicate the need for careful observation of persons so treated.

Mechanism of Action. The effect on blood lipids of nicotinic acid, a component of coenzymes I and II, was studied initially by Altschul [*39*] because of his earlier observations that increased oxidative processes diminished the concentration of serum cholesterol. Large doses were then employed following the observations of Hoffer and associates [*40*] that no toxic effects were encountered when such doses were used in the treatment of schizophrenia. Initially, Altschul and associates [*1*] postulated that nicotinic acid caused increased *in vivo* oxidation of cholesterol, leading to the formation of oxycholesterols, which were more readily excreted. Hoffer and Callbeck [*41*] suggested that nicotinic acid in large doses, by producing a relative deficiency of methyl groups in its conversion to N_1-methylnicotinamide, led to decreased production of epinephrine, and thus altered cholesterol metabolism. However, neither of these theories explained the lack of effect of nicotinamide in similar doses. Altschul and Hoffer [*22*] reported a slight increase in metabolic rate during administration of large doses of nicotinic acid to healthy volunteers, but there is no evidence that the hypocholesteremic effect of nicotinic acid is mediated in this fashion.

Kraupp and associates [*42–44*] have suggested that the hypocholesteremic effect of nicotinic acid may be mediated through saturation of the reticuloendothelial system with cholesterol or that possibly interference with the chemical quantitation of serum cholesterol leads to false, low values. Friedman and Byers [*45*], on the basis of their experience with nicotinic acid as a hypocholesteremic agent in the rat and rabbit, have concluded that its effect is mediated through anorexia-induced dietary changes. Recent data reported by Duncan and Best [*46*] support this finding in regard to rats. Our data do not support this theory in either man or the rabbit, and Altschul and Hoffer [*23*] have reviewed the considerable evidence in opposition to such a mode of action.

Several studies concerning the rate of incorporation of C^{14}-labeled acetate into cholesterol by the liver of animals both *in vivo* and *in vitro* have indicated a decrease in synthesis of cholesterol in the presence of large amounts of nicotinic acid [*47–50*]. Kritchevsky and co-workers [*51*] demonstrated that nicotinic acid also increased the oxidation of cholesterol by the mitochondria from hepatic cells of the rat. Clinical studies [*1,18,52*] have established the absence of effect on cholesterol metabolism by nicotinamide, and this fact has stimulated studies regarding differences in the metabolism of nicotinic acid and nicotinamide. Miller and associates [*31*] observed that in man approximately 20 to 25 per cent of nicotinic acid is combined with glycine and excreted as nicotinuric acid, whereas no nicotinamide is so converted. This observation has led to speculation that the nicotinuric acid so produced may be the substance that actually induced a decrease of serum cholesterol. In our experience with a small number of patients, nicotinuric acid, in oral doses similar to those of nicotinic acid, was ineffective.

More recently, observations by Schön [*50*] and by Schade and Saltman [*49*] have furnished another possible method of action of nicotinic acid on cholesterol metabolism. Their studies indicated marked depression of hepatic synthesis of cholesterol from C^{14}-labeled acetate by dietary nicotinic acid in both control and cholesterol-fed animals. Furthermore, the depression of synthesis was directly related to the percentage of nicotinic acid in the diets of the animals. The synthesis of fatty acids and of cholesterol from acetate is dependent upon coenzyme A. Substances such as α-phenylbutyric acid which require coenzyme A in their detoxication have been shown to inhibit synthesis of lipid from acetate [*53,54*]. The previously mentioned conversion of nicotinic acid to nicotinuric acid requires not only glycine and adenosinetriphosphate but also coenzyme A [*49*]. Hence, a mechanism involving effective competition with the system for synthesis of cholesterol for a limited pool of free coenzyme A possibly could account for the cholesterol-decreasing effect of nicotinic acid and the absence of effect of nicotinamide [*49,55,56*]. In dogs a combination of nicotinic acid and phenylethylacetic acid amide produces a greater

decrease in blood cholesterol than does either agent used separately [*57*]. A deficiency of pantothenic acid, a component of coenzyme A, has been induced in man by means of diets [*58*]. Although a decrease in the level of cholesterol in the blood was observed, it was believed related to changes in the source of fat in the diet employed [*53,58*]. It is of interest that a marked increase in sensitivity to insulin was associated with the deficiency of pantothenic acid, and hyperglycemia was not observed [*58*]. The hypothesis relating the hypocholesteremic effect of large doses of nicotinic acid to depletion of coenzyme A warrants further study. Knowledge of the precise mechanism of action is certainly needed so that the use of nicotinic acid in the treatment of hypercholesteremia can be given a sounder physiologic basis.

SUMMARY

Nicotinic acid, in doses of 1.5 to 6 gm. a day by mouth, has been administered to sixty-six persons with hypercholesteremia. A direct dose-response relationship was demonstrated. Eighty per cent of the fifty-one persons treated for at least one year, whose mean pretreatment value for plasma cholesterol was 327 mg. per 100 ml., had a mean value of less than 250 mg. per 100 ml. for plasma cholesterol during the three month interval of optimal response. The hypocholesteremic effect of nicotinic acid was sustained with continued treatment and was associated with a decrease of fatty acids and of the ratio of cholesterol to phospholipid in the plasma. Although subjective improvement in respect to symptoms of coronary and peripheral arterial insufficiency was noted by many persons during treatment with nicotinic acid, objective evidence of improvement in regard to clinical signs of atherosclerosis was lacking, and death from the complications of atherosclerosis occurred in eleven persons during or after treatment.

Side effects, particularly gastrointestinal irritation and cutaneous flushing, abnormal results in tests of hepatic function and carbohydrate tolerance, occurrence of hyperuricemia and, more rarely, of jaundice, have been associated with use of large doses of nicotinic acid.

The mechanism by which this substance decreases plasma lipids or causes many of the side effects noted is unknown.

The continued careful use of this agent in the investigative treatment of hypercholesteremia is warranted and may ultimately provide insight into the possible value of lowering elevated levels of cholesterol in the blood as a means of treatment or prevention of atherosclerosis.

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Hereditary Cardiovascular Dysplasia*

A Form of Familial Cardiomyopathy

J. A. P. Paré, M.D., Robert G. Fraser, M.D., F.R.C.P. (C)., W. J. Pirozynski, M.D., John A. Shanks, M.D., F.R.C.P. (C). *and* David Stubington, M.B., F.R.C.P. (C).

Montreal, Canada

A small proportion of patients dying suddenly, or following an episode of heart failure, is found at autopsy to show hypertrophy and fibrosis of the myocardium without evidence of significant valvular, hypertensive or coronary artery disease. In some cases it is assumed that the hypertrophy is due to unrecognized hypertension and that the blood pressure has fallen to within normal limits in the terminal stage of heart failure. In others, an excessive alcohol intake is considered to be responsible for the cardiomegaly. In still others, the hypertrophied and fibrotic myocardium is only part of a generalized disease, such as Friedreich's ataxia [*1,2*] or progressive muscular dystrophy [*3–6*], and the diagnosis is readily made on clinical grounds. There remains a small group of cases of undetermined origin in which the manifestations of disease are confined to the heart. These cases are labelled as idiopathic cardiac hypertrophy, or heart disease of unknown cause, and their pathogenesis remains obscure and the subject of much speculation [*7–11*].

In recent years, idiopathic cardiac hypertrophy has been reported to show a familial incidence which may extend over several generations [*9,13–30,34*]. Our interest in this condition began in the Fall of 1957 following the coincidental admission to hospital of two brothers, aged thirty-nine and forty-one years, (Cases 11 and 12) with unexplained cardiomegaly. In addition to their large hearts these two brothers showed evidence of cerebral damage which was considered to be on a vascular basis. An unusual incidence of sudden death and cerebrovascular accidents in other members of the family led us to suppose that this condition might be familial in nature. With this possibility in mind, we examined seventy-seven members of the family during the following two years. Complete histories were obtained and physical, electrocardiographic and radiologic examinations performed; these were repeated one year later on the majority of those subjects who had shown abnormalities on the initial screening. In addition, all available information was obtained on those members of the family who had already died.

The results of this survey are summarized in the form of a genealogical chart. (Fig. 1.) Of the seventy-seven persons examined, twenty were considered to have heart disease, and fifty-seven showed no abnormality. In addition, histories obtained on the deceased members of the family strongly suggested that another ten had died of heart disease. Thus a total of thirty members of the family are considered affected, and their case reports are summarized at the end of the paper. Cases 1 to 10 inclusive represent those persons who died before the study was initiated. In two of these we were able to obtain electrocardiograms which substantiated the histories of heart disease obtained from relatives. The remaining eight either had symptoms suggesting heart disease or had died suddenly at an early age.

Since the beginning of the study in 1957, five deaths have occurred among members of the family who had been examined, and autopsies were performed on three of these. In none of the ten members (Cases 1 to 10) who are believed to have died of the disease before this investigation began was a postmortem examination made.

Genealogy. A ninety-five year old member of the family supplied us with much of the early

* From the Departments of Medicine and Radiology, Royal Victoria Hospital and McGill University, and the Department of Pathology, McGill University, Montreal, Canada. This study was made possible by a grant from the National Heart Foundation of Canada.

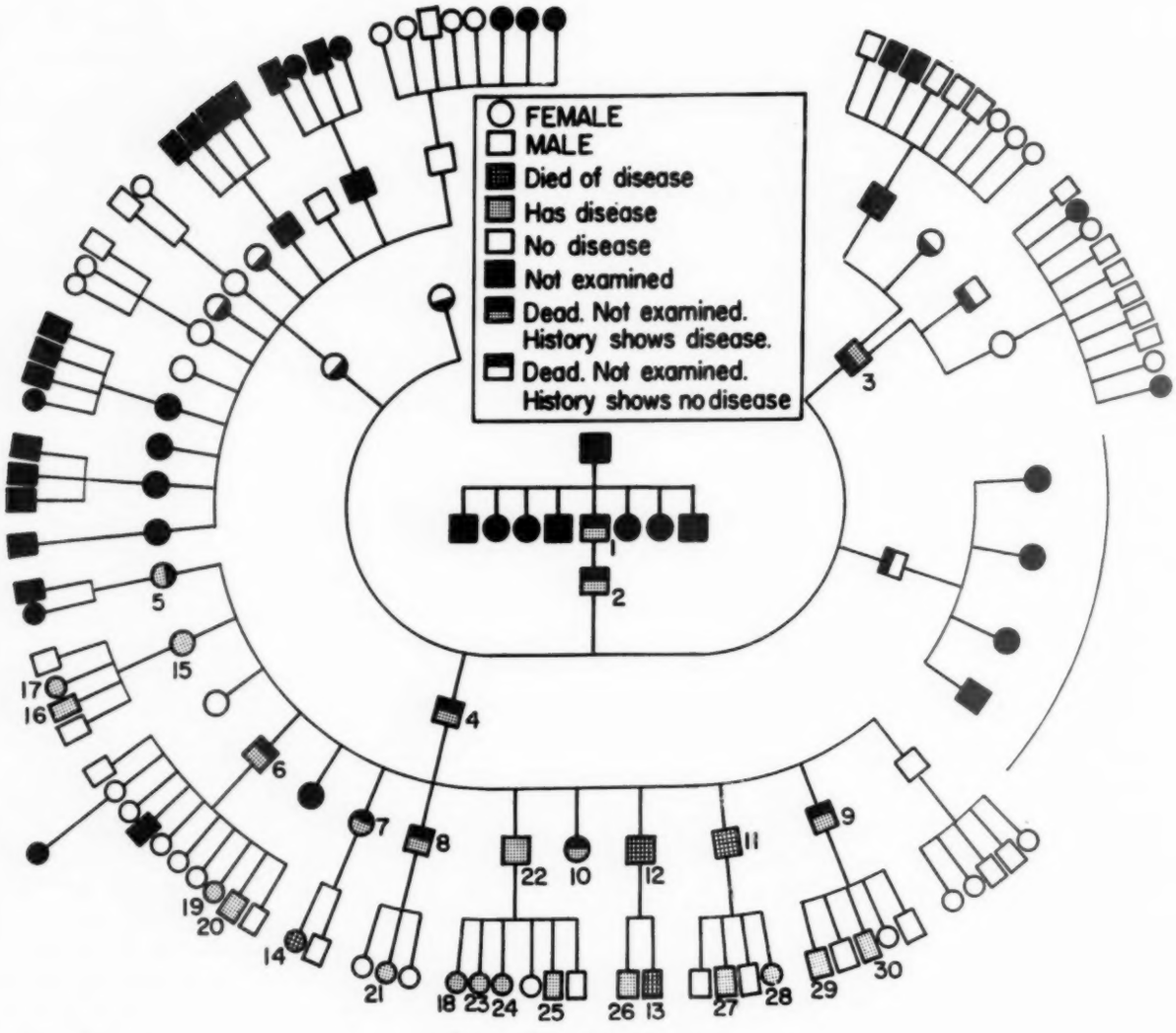

FIG. 1. Genealogical chart.

history, including that of his uncle's sudden death in 1860 (Case 1), and a description of his cousin's heart disease and early death (Case 2). This aged man, who had an excellent memory, was not aware of any other sudden deaths or heart disease in his uncles or aunts, and remembered them as having lived beyond the fiftieth year with the sole exception of the uncle (Case 1) whom we believe to have had the first case of heart disease in this family. (Fig. 1.) The son of this man (Case 2), an only child, had five offspring, and sudden death and heart disease were described as having occurred in two of his sons (Cases 3 and 4). One (Case 3) died suddenly while working on his farm: he had married twice and had twenty-three descendants. We examined sixteen members of this particular branch of the family without obtaining any evidence of heart disease. A sister of this man died at the age of sixty-four years in a mental institution and was not known to have had heart disease. A second sister died at the age of seventy and showed auricular fibrillation and peripheral embolism at the time of her death; fifteen of her forty-two descendants have been examined and are considered to have normal hearts. A brother emigrated to the United States, where he died at the age of seventy from a cerebrovascular accident. We have not examined this man's progeny as yet but have obtained information through correspondence which has led us to believe that they enjoy good health. The other brother (Case 4), who was disabled from a heart condition and died at the age of forty-six years, is the ancestor of the remaining twenty-six persons who are considered to have cardiac disease.

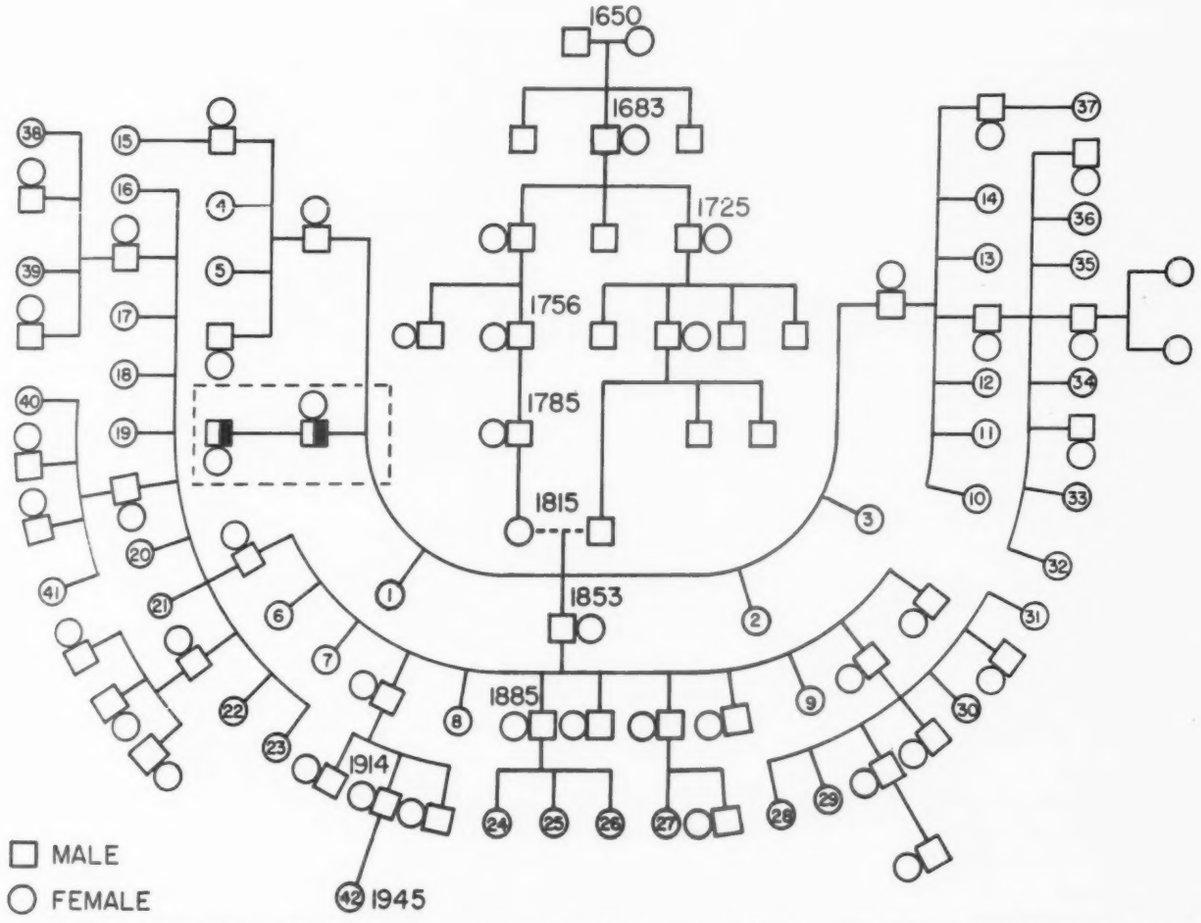

FIG. 2. Genealogical chart. A marriage date is shown in each generation. The rectangular area within the broken lines contains Cases 1 and 2 whose complete line of descent is shown in Figure 1. The numbers in the circles refer to a separate list of married names for follow-up purposes.

Forty-six members of this branch of the family have been examined; twenty have been found to have cardiac abnormalities leading to death in five instances.

While in the process of investigating this family tree we were presented with a genealogical survey of French Canadian marriages in the lower St. Lawrence region [*12*]. With this additional information we were able to draw up a more complete family tree which dated back to the original immigrant from France who was married in the Province of Quebec in 1650. (Fig. 2.) It will be seen that the original man with heart disease was the offspring of a marriage of two cousins once removed, and that three brothers and three sisters were also married and had numerous descendants. From this survey we obtained the married names of the female members of this family. This information may prove useful in the future to determine the relationship to our own family of other family groups showing heart disease.

Symptoms. The main symptoms and physical signs found in the affected members of the family are shown in Table I. The available data on those who already had died of heart disease are recorded in Table II.

Shortness of breath was the most common complaint. In most patients it was first noted in early childhood (Cases 13, 14, 17 and 21), but in those living to the fourth decade it did not usually appear until a few months before death (Cases 4, 6, 8, 9, 11 and 12). Weakness was another common symptom but its association with dyspnoea made its evaluation difficult. Transitory episodes of confusion, weakness and giddiness were complained of and were often described as a sensation of "blackness before the eyes." In seven cases this symptom was associated with syncopal attacks, usually precipitated

TABLE I

SUMMARY OF DATA ON THE PATIENTS STUDIED

Case No.	Sex	Age (1958) (yr.)	Symptoms					Signs						Electrocardiogram					Roentgeongrams							Cholesterol (mg. %)	Notes
			Dyspnoea	Weakness	Syncope	Palpitation	Cough	Systolic Thrill	Double Apex Impulse	Atrial Sound	Third Sound	Systolic Murmur	Diastolic Murmur	Abnormal P Wave	High QRS Voltage	Intraventricular Block	Abnormal Q Wave	Abnormal S-T or T (Lone)	Right Atrium	Right Ventricle	Left Atrium	Left Ventricle	Small Aorta	A-V Notch	Pulmonary Congestion		
11	M	39	+	+		+	+			+			+	+		+			2	2	2	3	+	+	+	110	CVA, DA
12	M	41	+	+									+	+		+	+			1	1	2	+	+	+	104	CVA, DA
13	M	17	+	+	+	+			+	+		3	+	+	+	+			±	±	1	1	+	+		112	B.P.$^{11}/_{0}$, D
14	F	19	+	+		+	+				+	3				+				1	1	2	+	+			DA
15	F	50	+	+		+				+								+									
16	M	17										1				+											
17	F	18	+	+	+	+	+					+	+	AF				+	2	2	2	2		+	+		?OS, D
18	F	17										1					+										
19	F	11								+	+							+		1	1	1					
20	M	10	+	+							+	3						+		1		1	±	+			
21	F	11	+	+						+		2	+					+	1	1	1	1	+	+		112	
22	M	43								+		2						+								212	
23	F	16	+								+						+			1	1	1		+		171	
24	F	14									+	1						+		1	1	1		+		204	
25	M	10	+	+							+	2								±	1	±				141	
26	M	15	+					+	+	+		4	+	+	+		+		1	1	1	1	+	+		153	
27	M	13	+		+							1						+									
28	F	18	+				+				+	2						+	1	1	±	1		+			
29	M	15	+	+	+	+	+		+	+	+	3	+	+				+	1	1	1	1	+	+		96	B.P.$^{12}/_{0}$
30	M	12	+		+			+	+	+		4	+		+	+			1	1	1	1	+	+		106	

NOTE: Systolic murmurs graded 1–6; chamber enlargement (x-ray) graded 1–3. D = Died. A = Autopsy. AF = Atrial fibrillation. OS = Opening snap. CVA = Cerebral vascular accident.

TABLE II

AVAILABLE DATA ON MEMBERS OF THE FAMILY WHO DIED PREMATURELY AND PRESUMABLY OF HEART DISEASE BEFORE OUR STUDY COMMENCED

Case No.	Age at Death (yr.)	Dyspnoea	Cerebral Vascular Accident	Sudden Death	Comments
1	30			+	
2	36	+		+	
3	37			+	
4	46	+	+		
5	45	+	+		Dropsy
6	40	+	+		Congestive failure, syncope, aortic diastolic murmur, A-V block and wide QRS
7	33	+		+	
8	43	+	+		Chest pain and haemoptysis, wide P waves, right bundle branch block
9	35	+	+	+	Blackouts
10	12	+		+	

by exertion. Three patients, aged thirty-nine, forty-one and forty-three, complained of chest pain, which was regarded as due to myocardial ischaemia. Gastrointestinal symptoms consisting of prolonged attacks of anorexia, nausea and vomiting were noted in five instances. Evidence of congestive failure was present in eight of the fifteen persons who died; eight died suddenly and did not display signs of cardiac decompensation preceding their deaths.

Physical Findings. On physical examination these people were found to be normally developed and of normal intelligence. This was as true of those who were restricted in their activity as it was of those who were asymptomatic. With the exception of slight scoliosis of the thoracic spine in two cases, polythelia in one, and the finding of chronic eczema in one branch of the family, the abnormalities were confined to the cardiovascular system.

A regular rhythm with a normal pulse rate was present in every case but one, an eighteen year old girl (Case 17) who had atrial fibrillation. Two others had occasional ventricular extrasystoles. The blood pressures were within normal limits with one exception (Case 13), in which there was a low diastolic pressure (110/40 mm. Hg).

In five patients cardiac enlargement was detected clinically. In four, a bifid apical impulse could be felt, the first lift occurring with a presystolic sound and the second with the usual first sound. Two patients had apical systolic thrills.

On auscultation, the first and second heart sounds were judged to be within the normal range. Nine subjects had an atrial sound at the apex, or at the lower left sternal border. This particular finding was noted in two of the five subjects who have died since our first examinations. A third heart sound was commonly heard but since most subjects were within an age group when this finding may be considered physiologic, its significance is doubtful.

Fifteen of the twenty patients examined had systolic murmurs which were usually widespread but of greatest intensity at the apex or in the lower sternal area. Clinically these were thought to be of the ejection type; this was confirmed by phonocardiography in three cases. (Fig. 3.) Two men (Cases 6 and 12) had early diastolic murmurs. In six instances, in addition to midsystolic murmurs, short, low-pitched, middiastolic murmurs were heard at the apex. These were clearly heard and were distinctly longer than a third heart sound.

Those subjects who were judged to have advanced disease on the basis of their symptoms, electrocardiographic and radiologic findings, usually showed most of these abnormal sounds and murmurs. (Fig. 3.)

Electrocardiographic Findings. Electrocardiograms (Fig. 4) were abnormal in all but one of the twenty members considered to have heart disease. In two instances the diagnosis was based on this finding alone (Cases 16 and 18). There was close correlation between strong clinical evidence for disease and gross changes in the electrocardiographic tracings.

Repeat electrocardiograms were obtained in thirteen patients one year following the initial examinations. In seven no significant changes were noted. In the remaining six the T waves in leads aVF and V_4 to V_7 had become flattened or inverted.

P waves: Atrial fibrillation was present in one patient (Case 17); in five others (Cases 11, 12, 13, 26 and 29) P waves were judged to be abnormal on the basis of high voltage and notching.

A-V conduction: The P-R interval was normal in all patients. Complete heart block appeared during the last few weeks of life in the patient who was fibrillating.

QRS complexes: QRS complexes were abnormal in nine tracings. Four showed complete bundle branch block, three left, and one right. In several patients an abnormal degree of QRS notching was present without widening of the complex.

In three, there was high voltage of the QRS complexes suggesting left ventricular hypertrophy. Four patients had deep and abnormally wide Q waves.

S-T segments and T waves: The S-T segments were depressed and sagging in the left chest leads in two patients, neither of whom was receiving digitalis.

The T waves were always abnormal. In most cases, flat or diphasic T waves were the only abnormalities recorded. (Fig. 4.)

Radiologic Considerations. All the members of the family were examined both fluoroscopically and radiographically. If the heart was judged to be abnormal on fluoroscopy, roentgenograms of the chest were obtained in posteroanterior, right and left anterior oblique, and lateral projections, within the oesophagus outlined by barium sulphate; those patients in whom the heart was regarded as normal only posteroanterior roentgenograms were obtained.

No significant abnormalities of the diaphragm or pulmonary parenchyma were observed, nor was there evidence of pleural effusion. In three patients (Cases 11, 12 and 17) there was pulmonary venous engorgement and mild pulmonary oedema as indicated by basal septal lines and by increased size and loss of definition of the pulmonary vasculature. The calibre of hilar and peripheral pulmonary arteries, how-

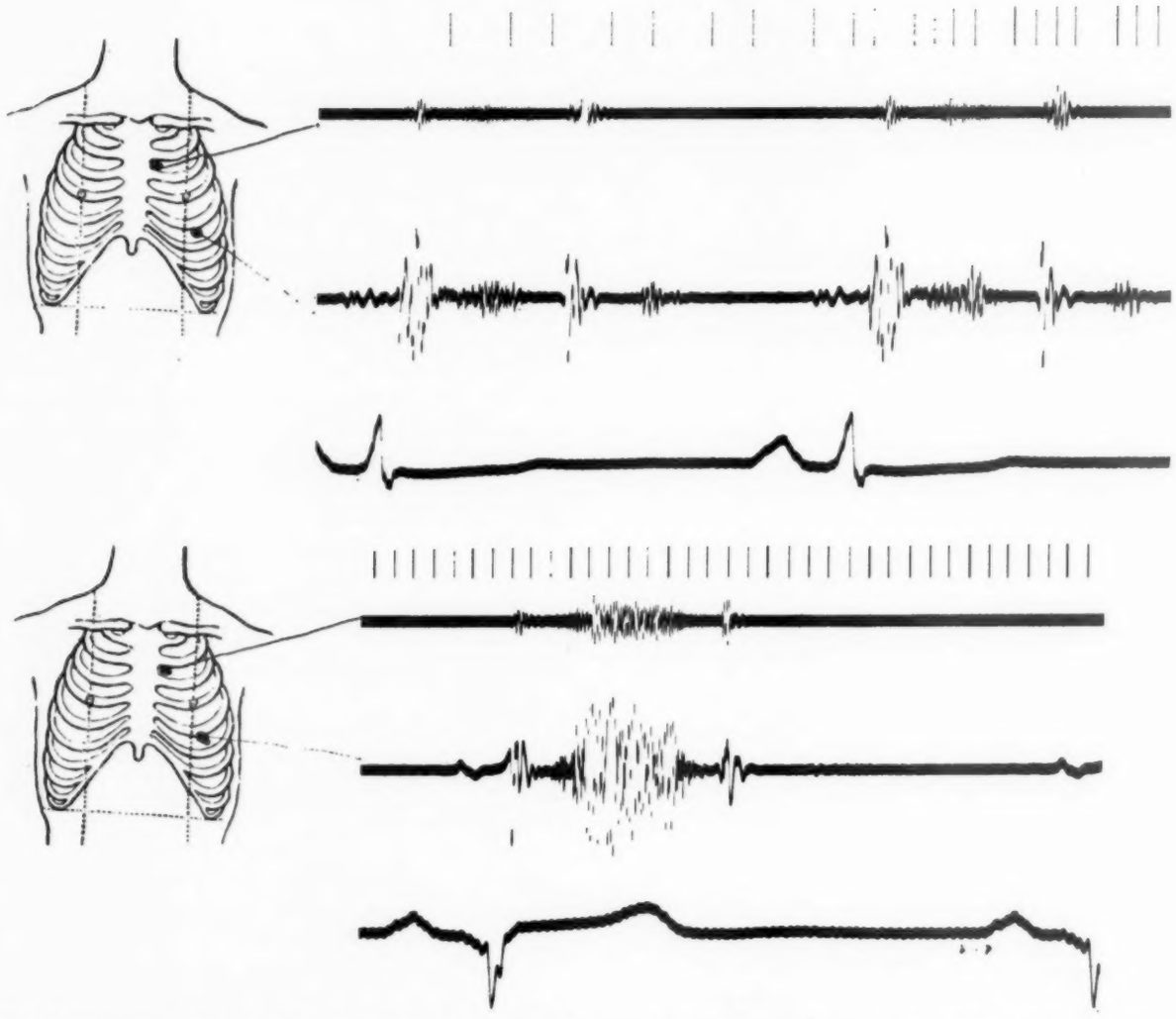

FIG. 3. Phonocardiograms. *Top*, Case 26. Note presystolic sound, ejection systolic murmur, mid-diastolic murmur. *Bottom*, Case 29. Note presystolic sound, ejection systolic murmur and mid-diastolic murmur.

ever, did not suggest the presence of pulmonary arterial hypertension.

Although the degree of cardiac enlargement varied to some extent in affected patients, alteration in contour showed considerable uniformity. In the majority, all chambers were judged to be enlarged (Figs. 5 and 6), although predominant enlargement was consistently left ventricular and left atrial. Although the apex of the heart was displaced slightly to the left and downwards, the main evidence for left ventricular hypertrophy was an outward bulging of its posterior surface, seen to best advantage in the left anterior oblique projection. When this left ventricular bulging was combined with the increased prominence of the left atrial shadow in this obliquity, the position of the atrioventricular junction was readily identifiable as an indentation or notch. (Figs. 5C, 6C and 7.) This notch was so distinctive as to be clearly visible in all but two of those with cardiomegaly (Cases 19 and 25); in these two only minimal cardiac enlargement was present.

Increased prominence of the anterior surface of the heart in the right anterior oblique projection was present in every patient with cardiomegaly and was interpreted as representing right ventricular hypertrophy.

The aorta (Figs. 5 and 6) was regarded as being of reduced calibre in eight patients. The amplitude of cardiac pulsation was normal, with the exception of a girl with atrial fibrillation (Case 17).

In twelve subjects an opportunity was af-

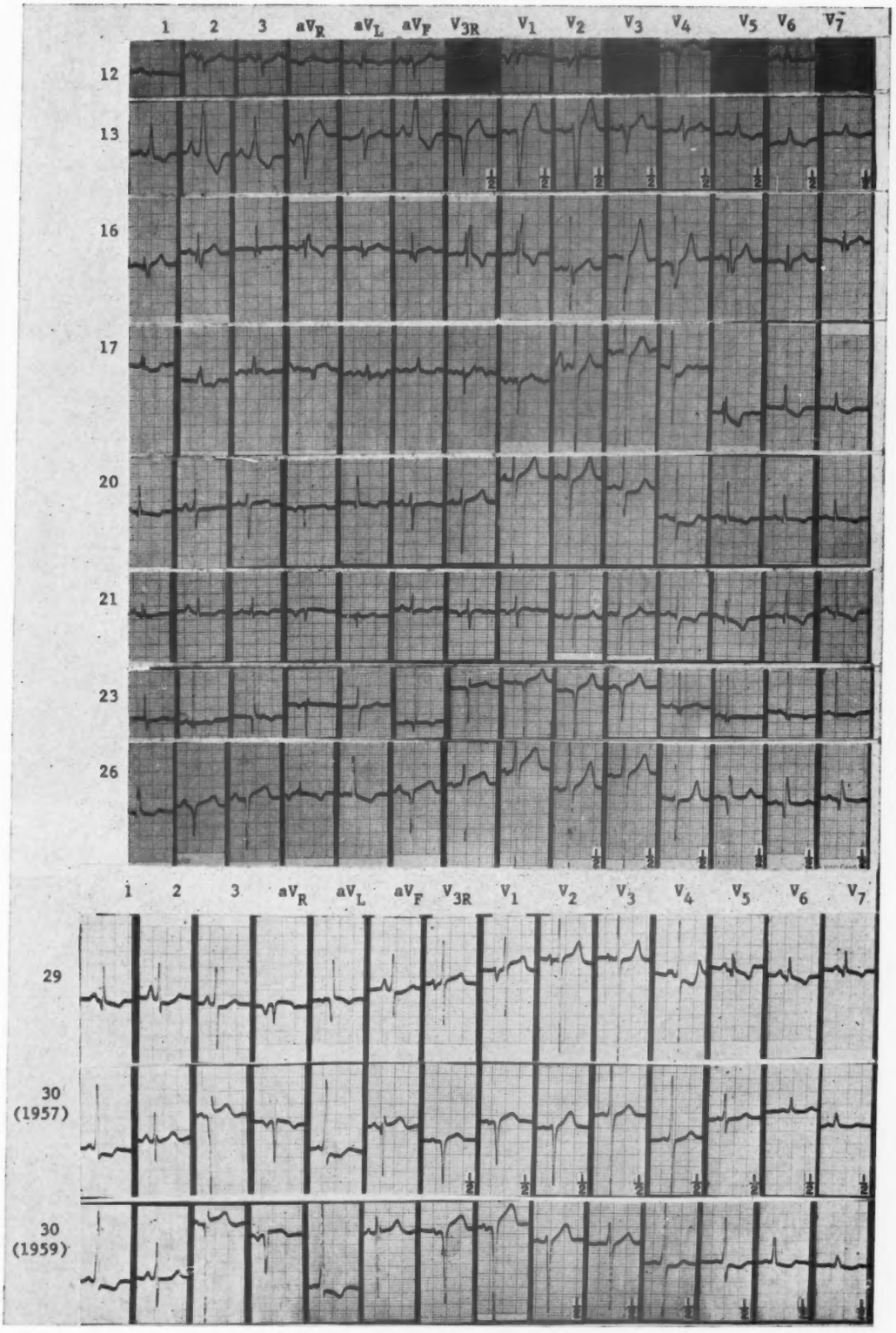

FIG. 4. Electrocardiograms.

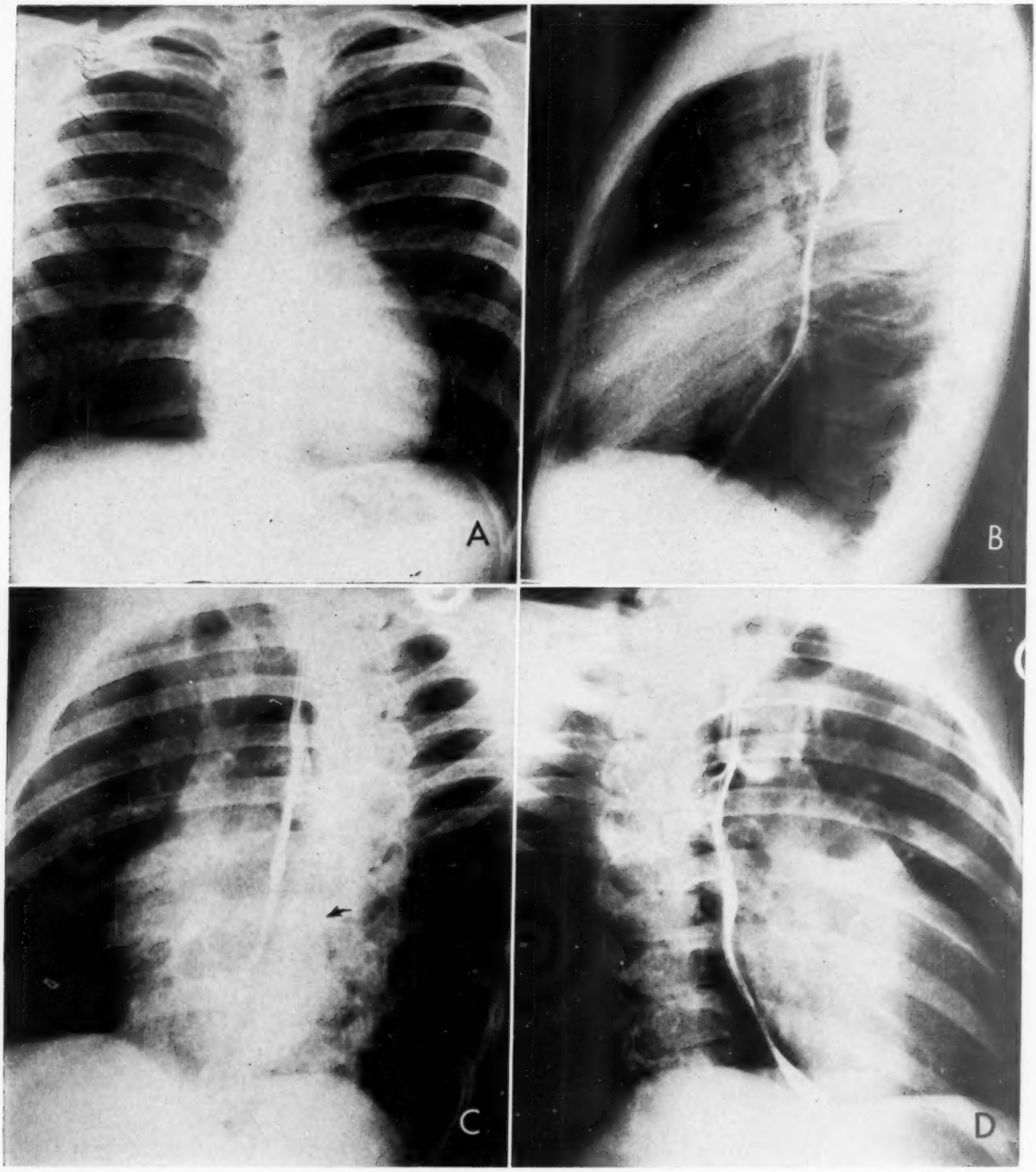

FIG. 5. Case 30. (A) posteroanterior, (B) lateral, (C) left anterior oblique and (D) right anterior oblique views of the chest. Note enlargement of all cardiac chambers, indentation on posterior surface of heart in (C) (*arrow*), representing left atrioventricular junction.

forded to re-examine the heart at one year's interval, and in four of these (Cases 21, 26, 28 and 30) definite enlargement had occurred during this period. The remainder showed no change.

In addition to fluoroscopic and roentgenographic examinations of the heart, tomograms of the lungs and roentgenograms of the skull were obtained in three young boys (Cases 26, 29 and 30). These procedures were carried out as part of a thorough examination to assess the pulmonary arterial calibre and to detect the

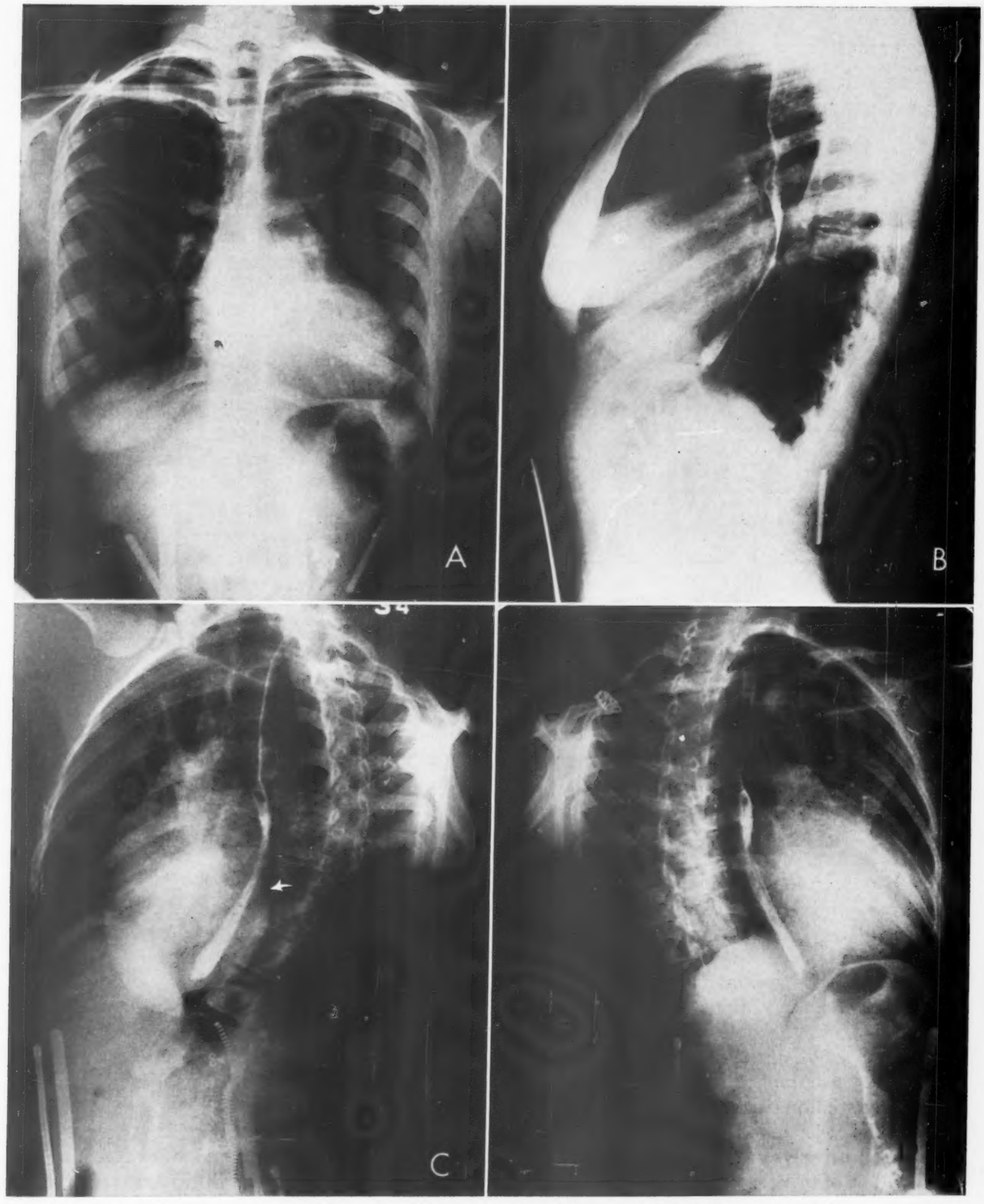

FIG. 6. Case 14. (A) posteroanterior, (B) lateral, (C) left anterior oblique and (D) right anterior oblique views of the chest. All cardiac chambers are enlarged. Note particularly indentation on posterior surface of heart in (C) (*arrow*), representing left atrioventricular junction. Compare with Figure 7.

TABLE III
MEASUREMENTS OF HEART (NORMAL VALUES INSERTED IN BRACKETS)

Area		Thickness (in mm.)		
		Case 11	Case 13	Case 14
Left ventricle	At the base	13 (8–10)	12 (8–10)	22 (8–10)
	Mid-portion	13–14 (10–12)	20 (10–21)	20 (10–12)
Right ventricle	At the base	5 (2–3)	7 (2–3)	5 (2–3)
	Mid-portion	4 (3–4)	8 (3–4)	5 (3–4)
Interventricular septum	At the base	11 (10–12)	32 (10–12)	30 (10–12)
	Mid-portion	10–11 (12–14)	26 (12–14)	26 (12–14)

presence of associated abnormalities. The roentgenograms of the skull and the central and peripheral pulmonary vessels were judged to be within normal limits.

Special Investigations. Five members of this family have been admitted to the Royal Victoria Hospital. In 1957 the two original patients (Cases 11 and 12) underwent a variety of laboratory procedures and the results of these tests were within normal limits, with the exception of the serum cholesterol levels which were low. (Table I.) In 1959, three younger boys (Cases 26, 29 and 30) were admitted for more complete investigation, and the following examinations were carried out: phonocardiograms; cardiac output by a dye method; brachial artery pulse tracings; pulmonary function tests; electroencephalograms; tuberculin, histoplasmin and toxoplasmin skin tests; blood volumes; blood cytology, including blood grouping; blood coagulograms; protein electrophoresis; serum electrolytes; serum cholesterol levels; blood sugars; blood Wassermann tests; urinalyses; twenty-four-hour amino acid content of urine.

Abnormal results included a lowered cardiac output in one patient (Case 29); slightly reduced vital and functional residual capacities in two (Cases 29 and 30); a paroxysmal dysrhythmia seen on the electroencephalogram of one (Case 29), and low serum cholesterol levels. Serum cholesterol levels were subsequently determined in six other members of the family, and were found to be low in two. Thus of the eleven in whom serum cholesterol levels were determined, six showed values well below the normal range. (Table I.) The brachial artery tracings were regarded as abnormal and are described subsequently and compared to those reported in the literature.

Pathologic Findings. Autopsies have been performed on three members of the family. A seventeen year old boy (Case 13) and a nineteen year old girl (Case 14) died suddenly without having shown any evidence of cardiac failure during life. A man of thirty-nine years (Case 11) died following recurrent cerebrovascular episodes which had rendered him aphasic and hemiplegic.

The autopsies on the two young people were performed after their bodies had been embalmed, with resultant alteration in the appearance of some organs. The pathologic findings in these two instances were remarkably similar and were confined to the cardiovascular system. The boy's heart weighed 575 gm., the girl's 505 gm. All chambers were hypertrophied (Table III), particularly the left ventricle, and in each case there was a peculiar nodular muscle mass in the cephalic two-thirds of the interventricular septum. (Figs. 9 and 10.) This hypertrophied myocardial mass bulged into both ventricular cavities and merged gradually with the more symmetrically hypertrophied muscle fibres in the apical portion of the septum. (Figs. 7, 8 and 11.) The papillary muscles and trabeculae carneae cordis were enlarged and elongated. The valves were normal and the endocardium smooth and transparent. Small and large irregular patchy areas of fibrosis were seen throughout the myocardium, especially in the left ventricle, papillary muscles and interventricular septum. (Figs. 9 and 10.) The coronary arteries showed no evidence of occlusion and were normal in distribution and calibre.

The microscopic findings in two patients (Cases 13 and 14) were identical. A marked hypertrophy of muscle fibres was noted. In addition, many of these fibres showed disintegration of cytoplasmic components and loss of striations; in some areas, only shadow structures of the sarcolemma remained. This process of transition from hypertrophied to disintegrated

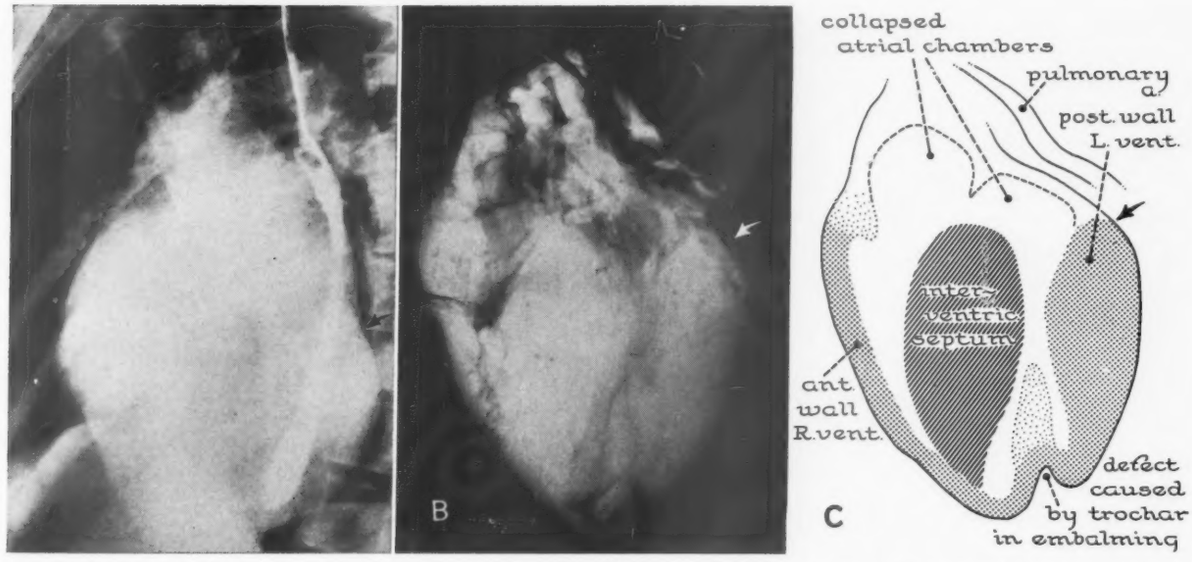

FIG. 7. Case 14. (A) left anterior oblique roentgenogram, (B) roentgenogram of gross specimen of heart in approximately same projection as in (A), (both atria are collapsed); (C) diagram of (B). Note generalized hypertrophy of left ventricle, localized muscle mass in cephalic portion of interventricular septum bulging into both left and right ventricular chambers and simulating hypertrophy of right ventricle, notch or indentation on posterior surface of heart in (A), corresponding to upper edge of hypertrophied left ventricular muscle mass in (B) (*arrows*).

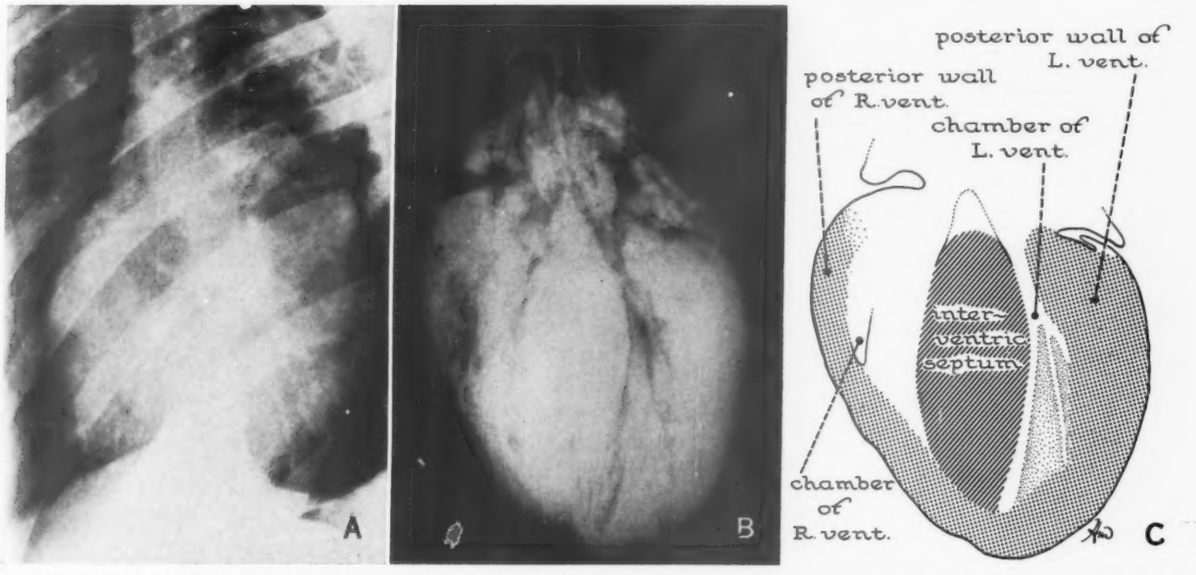

FIG. 8. Case 13. (A) left anterior oblique roentgenogram, (B) roentgenogram of gross specimen of heart in approximately same projection as in (A) (both atria are collapsed), (C) diagram of (B). Generalized hypertrophy of left ventricle is marked but the asymmetrical muscle mass in cephalic portion of interventricular septum is not as striking as in Case 14, Figure 7.

fibre occurred gradually, without any sharp delineation. (Fig. 12.) In the left ventricle, and particularly in the nodular mass of the interventricular septum, there were areas where the muscle fibres formed an interdigitating network of "Y" shaped and semicircular bundles in a peculiar haphazard architectural pattern. In these areas, loosely arranged connective tissue, which included blood vessels, was seen to lie between these muscle bundles. (Figs. 13 and 14.) Throughout the myocardium there were irregular areas of fibrosis. (Fig. 15.) No

FIG. 9

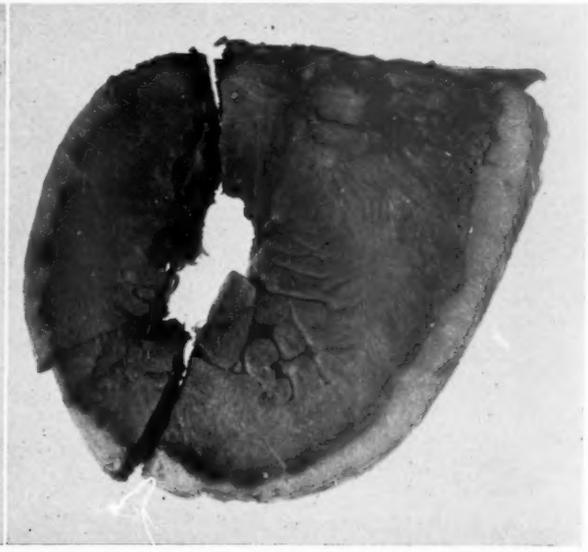

FIG. 10

FIG. 9. Case 13. Coronal section of the heart showing hypertrophy of both ventricles and a muscular mass in the interventricular septum. Multiple areas of fibrosis are scattered throughout the myocardium.

FIG. 10. Case 14. Coronal section of heart showing hypertrophy of the left ventricle with a muscular mass in the interventricular septum. There is distortion of both ventricles caused by the embalming process.

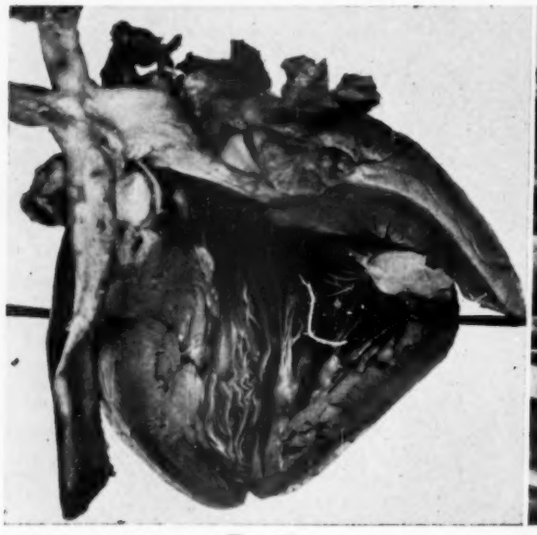

FIG. 11

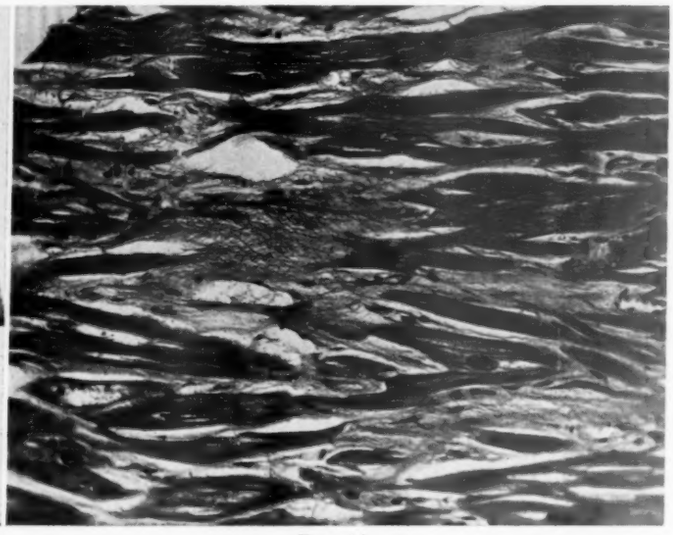

FIG. 12

FIG. 11. Case 13. The heart with an opened left ventricle showing hypertrophy of the myocardium. Muscular mass of the interventricular septum bulges into the ventricle.

FIG. 12. Case 13. Section through the myocardium of the left ventricle. There is disintegration of muscle fibres with replacement by connective tissue. Hematoxylin and eosin stain.

inflammatory reaction of any type was found in multiple sections.

The third autopsy was performed on a thirty-nine year old man (Case 11) whose heart weighed 680 gm., after fixation. (Fig. 16.) There was dilatation of all heart chambers and concentric hypertrophy of the left ventricle. (Table III.) The localized hypertrophy of the interventricular septum seen in the two other patients was not observed. Many large areas of fibrosis were scattered throughout the left ventricular myocardium. These fibrotic areas tended to

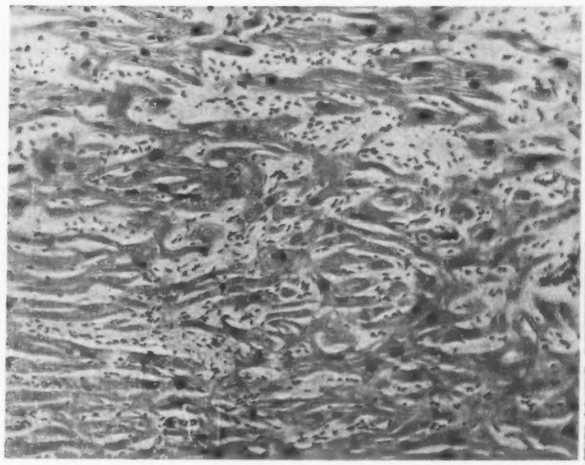

FIG. 13

FIG. 14

FIG. 13. Case 14. Section through the myocardium of the left ventricle. Muscle fibres are hypertrophic and separated by loose connective tissue. Hematoxylin and eosin stain.

FIG. 14. Case 13. Section through the myocardium of the left ventricle showing bizarre arrangement of intertwining muscle fibres which are separated by loose connective tissue. Hematoxylin and eosin stain.

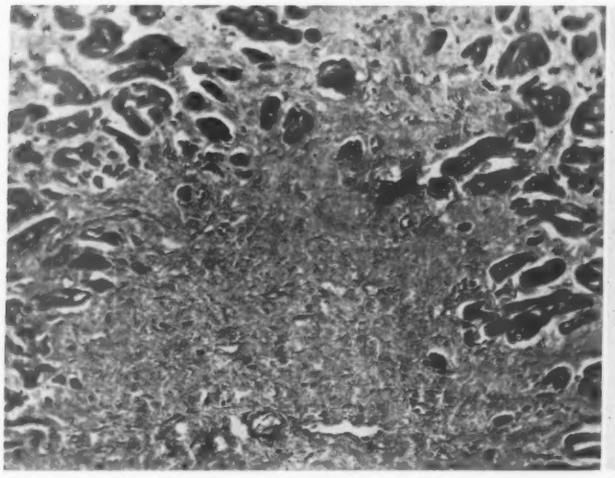

FIG. 15

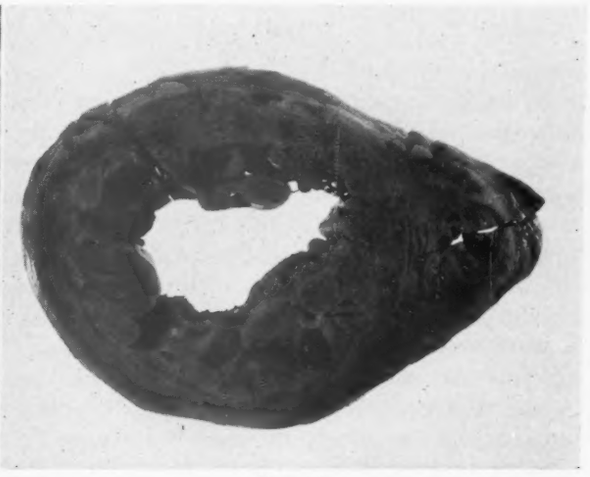

FIG. 16

FIG. 15. Case 13. Section through the myocardium of the left ventricle. There is a large area of fibrosis and hypertrophy of muscle fibres. Hematoxylin and eosin stain.

FIG. 16. Case 11. Coronal section of the heart showing hypertrophy of the myocardium with multiple areas of fibrosis and mural thrombi.

coalesce toward the apex on the anterior aspect of the left ventricle and interventricular septum, where the endocardium was also thickened and fibrosed, with firmly attached mural thrombi. There was slight non-specific thickening of the anterior leaflet of the mitral valve which had not resulted in any stenosis. The other valves were normal in appearance. The coronary arteries were patent throughout although there was a mild degree of arteriosclerosis.

On microscopic examination the myocardial fibres were hypertrophied and in some places disintegrated and replaced by fibrous tissue. The bizarre architectural pattern seen in the other two patients was not present. Organized and organizing mural thrombi were attached to the area of thickened endocardium at the apex.

The lungs, kidneys, brain and intestines showed evidence of old and recent infarcts.

All three subjects showed hypoplasia of the aorta (Table IV) and medium-sized arteries, with slight intimal arteriosclerosis. There was

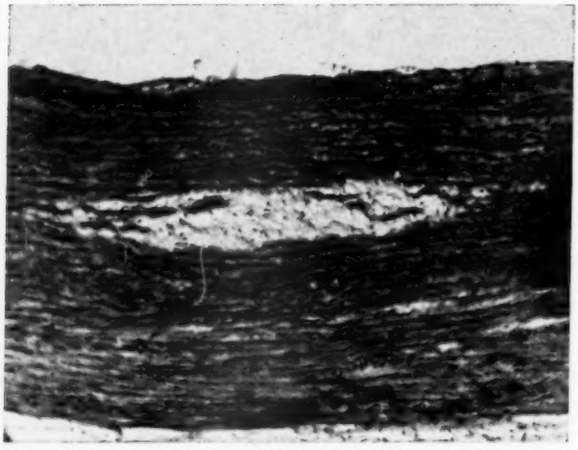

FIG. 17. Case 14. Section of the abdominal aorta. There is focal accumulation of slightly basophilic mucoid substance in the media. Hematoxylin and eosin stain.

TABLE IV
MEASUREMENTS OF AORTA (NORMAL VALUES* INSERTED IN PARENTHESES)

Area	Circumference (in mm.)		
	Case 11	Case 13	Case 14
Above valve	52 (73)	40 (57)	40 (55)
Underneath arch	45 (54)	35 (44)	30 (43)
At diaphragm	45 (53)	23 (40)	34 (39)
Above bifurcation	26 (41)	20 (31)	(29)

* After KANI, J. Tabulae Biologicae, vol. 3. Berlin, 1926. Junk.

atrophy and degeneration of the muscle coats with increase in collagen and accumulation of basophilic mucoid substances. (Fig. 17.)

COMMENTS ON HEREDITARY CARDIOVASCULAR DYSPLASIA

Heart disease has been found to occur in approximately 50 per cent of the children of any afflicted member of this family, independent of sex. Our original suspicion that such a large number of cases in one family might represent a hereditary form of cardiac disease is borne out by this non-sex-linked Mendelian dominant pattern of transmission. The pathologic evidence is consistent with a defect in the embryologic development of the cardiovascular system. The localized massive hypertrophy of the cephalic portion of the interventricular septum, the bizarre disorganized architecture of the myocardial fibres, and the hypoplasia of the aorta and large arteries are not characteristic of any acquired heart disease.

In recent years the medical literature has contained an ever increasing number of descriptions of familial and hereditary heart disease, some of which bear a resemblance to our own cases. The first reference to myocardial disease in a family was made in 1946 by Addarii et al. [*13*], who described bundle branch block and cardiac failure in two brothers whose mother had died from heart disease at the age of thirty-four years. Postmortem examination of one of the brothers revealed hypertrophy and diffuse fibrosis of the myocardium and hypoplasia of the aorta. In 1949 William Evans [*14*] described a group of ten patients with idiopathic cardiac hypertrophy. He introduced the term "familial cardiomegaly," since five of his patients were members of two separate families. During the last decade many other reports of familial heart disease have appeared. In some instances the evidence has been based on clinical examination only [*9,21,23–27*], but in most cases autopsies have been performed and have been found to show myocardial hypertrophy and fibrosis [*15–20,22,28–30,34*]. Although there is considerable variation in the clinical picture in these reported series, two features are common to all: A familial occurrence which in some cases can be traced over several generations and, in those cases in which autopsy was performed, the invariable finding of hypertrophy and fibrosis of the myocardium.

In the series previously reported the number of cases involved has not been sufficient to establish a genetic pattern. Brigden [*27*], in reviewing the non-coronary cardiomyopathies, has stated that the published reports of familial cardiomegaly suggest a Mendelian dominant mode of transmission. More recently Brent et al. [*30*] have described a familial subaortic stenosis in which the family pedigrees indicate a dominant inheritance.

Familial myocardial disease is usually described as occurring in the second or third decades, and the majority of our own patients fell into these age groups. We did not obtain a history of frequent infant death to suggest that a more severe degree of developmental defect might exist, although it is possible that the dis-

ease did not occur in the descendants of our patient (Case 3) due to the deaths in early infancy of two of his offspring. In our own cases it has been more the rule than the exception to live to a marriageable age, and this has resulted, over three generations, in a sixteenfold increase in the number of cases. Similarly, there does not appear to be any clear-cut evidence of the disease occurring at an earlier age in succeeding generations (phenomenon of anticipation) or of it being manifested in more severe forms (phenomenon of potentiation). Most of the children in our series are not seriously disabled and it would seem likely that they will live as long as their afflicted ancestors.

In at least some instances familial myocardial disease appears to be relatively benign and there have been descriptions of older people in the sixth or seventh decade showing little in the way of disability. Soulie and his associates [*22*] include in their report a fifty-four year old man, followed up over a two year period, who had a transitory episode of right hemiplegia and aphasia and subsequently died suddenly. Facquet et al. [*24*] report a mild form of familial cardiomegaly and describe a woman showing a minor degree of heart failure at the age of fifty-seven, whose eight children were affected, all of whom were asymptomatic. She also had a brother, fifty-three years of age, who had electrocardiographic and radiologic evidence of heart disease and who was completely asymptomatic. The second family, described by Campbell and Turner-Warwick [*17*], included two women of sixty-six and sixty-nine years of age, both of whom were considered to suffer from familial heart disease. In our own series the finding of abnormal electrocardiograms in two adults (Cases 15 and 22) with little or no disability suggests that minor involvement may be quite compatible with a relatively normal life span. The occurrence of this heart disease in adults free or almost free from symptoms raises the possibility that the brothers and sisters of our patient (Case 1) may also have been affected and that their descendants may eventually prove to have the disease.

The clinical picture presented by members of this family did not differ materially from that of rheumatic endocarditis, and several of the children had been considered to have valvular disease when seen individually by cardiologists. Dyspnoea was the most common symptom; the severity and the age of onset of this complaint varied considerably from case to case. Some members of the family attained adulthood before noticing shortness of breath, while others were disabled from early childhood. Sudden brief episodes of loss of consciousness, usually brought on by physical activity, were common occurrences. Syncopal attacks, sudden death [*14,15, 17–19,22,30*] and cerebrovascular accidents ascribed to embolization from mural thrombi [*18,22,28*] have occurred commonly in previously reported instances of familial heart disease. In some descriptions these syncopal attacks have been noted to occur in subjects with complete heart block [*16,17*], but more often they have not been associated with any obvious conduction defect and have been of a transitory nature, frequently coming on following exertion.

Electrocardiography proved to be the most sensitive means of detecting the disease in this group. In some cases the tracings were judged to be abnormal on the basis of changes in the T wave alone. The assumption that this could represent an hereditary myocardial disease in an eleven year old boy (Case 20) seems reasonable. On the other hand such changes in adults (Cases 15 and 22) could be explained by myocardial ischaemia secondary to coronary artery disease, and for this reason the diagnosis of primary myocardial disease in these two subjects is slightly suspect. The more bizarre electrocardiographic patterns were found in those who had clinical evidence of a more severe form of the disease. High amplitude of the QRS complexes, pathologic Q waves, and varying degrees of bundle branch block were commonly seen. In contradistinction to our own findings, the literature on familial heart disease reveals arrhythmias to be a rather common feature. Sinus bradycardia [*14,17*] and nodal rhythms [*15,17*] have been described, as well as auricular fibrillation and flutter [*14,17,19,22,29*]. Varying degrees of partial A-V block [*14,17,20–23,40*], and a few cases of complete atrioventricular block [*14,16,17*] and Wolff-Parkinson-White syndrome [*22*] have been noted. The most characteristic electrocardiographic findings, however, have been bundle branch blocks [*14,17,18, 22,23,25,28*] and a high amplitude of the QRS complexes in the pattern of left ventricular hypertrophy [*16,22,24–26,29,34*].

Radiologic examination of the heart revealed cardiomegaly in fifteen of the twenty patients. Although the cardiac enlargement appeared to involve all chambers of the heart, the

left ventricle and left atrium were predominantly affected. A very characteristic finding seen in all but two of those patients showing cardiomegaly was an indentation visible in the left anterior oblique projection and considered to represent the atrioventricular junction between hypertrophied left atrium and left ventricle. This indentation has also been noted occasionally in patients with rheumatic mitral valvular disease with combined stenosis and insufficiency, but not as commonly as was observed in this group of patients. The prominence of the anterior surface of the heart in the right anterior oblique projection, found in almost every patient with cardiomegaly, was interpreted as representing right ventricular hypertrophy. The subsequent autopsies, however, revealed only minimal right ventricular hypertrophy, and our erroneous interpretation of enlargement of this chamber was readily explained by the large interventricular septal mass bulging forward and producing a prominent anterior cardiac wall.

The results of the laboratory procedures on the patients whom we admitted to hospital were not particularly revealing. The finding of low serum cholesterol levels in some of the patients was unexpected and it is perhaps of some significance that all patients showing hypocholesterolemia were considered clinically to have evidence of a more severe disease. The values obtained are in the range seen only in hyperthyroidism or in advanced liver disease, and none of these patients showed evidence of either of these two conditions. Although liver function tests were not obtained as an investigative procedure, one of the patients (Case 13) with a serum cholesterol level of 112 mg. per cent, subsequently died; his liver was found to be normal at postmortem examination. Similarly, in previously reported series, little information has been obtained from laboratory procedures. Serum cholesterol levels have been measured occasionally and in some instances have been found to be within the normal range [*30*], although it is of interest that in two case reports [*20,43*] serum cholesterol levels were abnormally low.

The localized muscular hypertrophy at the base of the septum in our two autopsy cases caused subaortic stenosis and this provides an explanation for the ejection systolic murmurs heard in the majority of cases. This assumption is supported by the absence of systolic murmurs in the third autopsy case, in which gross septal hypertrophy was not evident. In addition, in some cases this muscular mass appears to interfere with the inflow of blood from the left atrium, producing a mid-diastolic murmur. The early diastolic murmurs are difficult to explain.

The hypertrophied muscular mass in the left ventricular outflow tract has become a well recognized pathologic entity, and there is reason to believe that this lesion may be acquired [*35*], although in most series the evidence suggests a congenital origin. Many cases do not show a familial incidence [*28,31–36*], but it appears to be a very characteristic finding in several families with heart disease. Evans [*14*] refers to a sixteen year old boy who showed a considerable enlargement "involving the base of the left ventricle" at autopsy. A thirty-eight year old female member of the family described by Davies [*15*] was found at autopsy to have an area of fibrosis 4 cm. square, located "on the upper part of the interventricular septum, behind the aortic cusp of the mitral valve." Teare [*28*] has described what he calls "asymmetrical hypertrophy" of the heart in three siblings, two of whom at autopsy showed globular-shaped hearts with hypertrophy of the interventricular septum and the anterior walls of the left ventricles. More recently Bercu et al. [*29*] have reported on "pseudo-aortic stenosis produced by ventricular hypertrophy." Brent et al. [*30*] have presented two families with "familial muscular subaortic stenosis," and Braunwald et al. [*32*] have described familial cases of "idiopathic hypertrophic subaortic stenosis." From the descriptions given in the literature this unusual pathologic finding is probably the same abnormality masquerading under a great many pseudonyms. It has been suggested that this obstructing lesion may be suspected and differentiated from valvular aortic stenosis on clinical grounds [*31,32,34*]. The ejection murmur is heard at the left sternal border, or at the cardiac apex, and not at the base of the heart. A palpable thrill may be detected over the same area but is not common. The peripheral arterial pulse is normal, but direct pulse tracings show a rapid upstroke time, sometimes followed by a second positive deflection, and not the slow rise to a peak, or the anacrotic notch of aortic stenosis [*31,32,34*]. Our own findings (including the brachial artery tracings, Figure 18) are in agreement with the reported clinical manifestations of subvalvular muscular stenosis. The rapid initial deflection in the pulse tracing, which is not seen in valvular aortic stenosis, is particularly

significant when a large pressure gradient can be demonstrated between the main cavity of the left ventricle and a systemic artery. Under these circumstances it is likely that symptoms will be present, and Braunwald et al. [*32*] suggest that operation is indicated. Additional confirmatory evidence that the patient has muscular obstruction rather than valvular stenosis can be obtained by left ventricular angiocardiography [*32,34*].

Our own patients were not subjected to pressure measurements across the aortic valve or to angiocardiography, since it was our opinion that the slight risk involved in carrying out these procedures was hardly justified in a group of subjects who were prone to sudden death and, as we thought, were not candidates for any remedial surgery. However, in view of the encouraging initial results in one patient reported by Goodwin et al. [*34*], and two cases reported by Braunwald [*32*], following an operation suggested by Cleland [*34*], we are at present making arrangements to carry out these additional diagnostic procedures on some of our family group prior to considering them for operation.

In some reports [*13,16–20,22,37*] of familial myocardial disease, the cardiac muscle has been found to be symmetrically hypertrophied and no mention is made of a localized mass in the interventricular septum. Our own pathologic findings indicate that even in the same family a diffuse form of myocardial hypertrophy may be found in some cases, and the interventricular septal hypertrophy be predominant in others.

Reference has also been made in the literature to endocardial thickening [*19,22*] but this pathologic change has been less impressive than the myocardial involvement and hence has received little emphasis. However, the literature also contains descriptions of combined endocardial and myocardial disease with a familial incidence [*37–39*], in which the former lesion has been predominant; such conditions have been referred to as endocardial fibroelastosis or endomyocardial sclerosis. Brigden [*27*] has ventured the opinion that this thickening of the endocardium may actually be due to organized thrombi which have become closely interwoven with the adjacent endocardium.

Microscopic examination in our cases showed hypertrophy of individual muscle fibres with scattered areas of fibrosis and degenerating myofibrils, without evidence of deposition of foreign substance or cellular infiltration. These findings

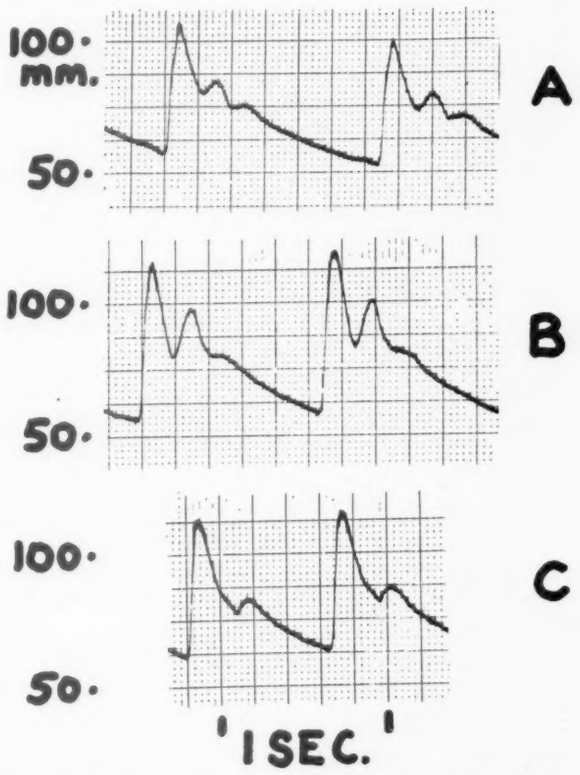

FIG. 18. Brachial pulse tracings. Note the normal upstroke time and the prominent secondary wave. A = Case 26, B = Case 30, C = Case 29.

are in keeping with the majority of published autopsy reports, although Evans [*14*] and Gaunt and Lecutier [*16*] found glycogen in the myocardium, and Sommers [*19*] and Nikkila and Pelkonen [*20*] have described cellular infiltration. Teare [*28*] has noted a bizarre arrangement of individual muscle bundles such as was found in two of our patients (Cases 13 and 14).

Hypoplasia of the aorta was detected radiologically in eight members of our family, and measurements made on three of these at autopsy confirmed this observation. (Table IV.) The association of aortic hypoplasia with familial myocardial disease has been previously noted either radiologically [*15,24,26*] or at postmortem [*15,19,43*]. Hayes et al. [*43*] stressed the finding of a hypoplastic aorta in their family, and described interventricular hypertrophy in a nineteen year old boy. The clinical picture manifested by this patient appears to be identical with that seen by us, even to the finding of a low serum cholestrol level. Microscopic examination of the aortas in our three cases revealed atrophy and degeneration of the media with an accumulation of mucoid basophilic material. A

similar deposition of foreign material is often found in cases of Marfan's syndrome, and it is of interest that this condition may also present as a cardiomyopathy. Whitfield et al. [*41*] have described a man with arachnodactyly, hypoplasia of the aorta, and myocardial hypertrophy and fibrosis. A familial form of this syndrome, with autopsies showing hypertrophied and fibrotic hearts, has also been reported [*40,42*].

The disease which we have described is considered to be the result of an inherited defect in development involving the myocardium and the media of larger arteries. Similar if not identical conditions have been reported under a variety of titles, none of which seems adequately to incorporate all significant features of the disease. The terms "familial cardiomegaly" and "familial or hereditary cardiomyopathy" do not take into account the fact that some patients fail to show cardiac enlargement or that the larger vessels may also be involved. In most other reported series of familial myocardial disease, interest has been focused on the localized interventricular hypertrophy with its resultant subaortic stenosis, and a great number of descriptive terms have been suggested for this lesion. In view of the lack of a suitable name for this well delineated clinical and pathologic entity, and recognizing the desirability of incorporating in the title some reference to the involvement of the larger blood vessels, we propose that this disease be known as "hereditary cardiovascular dysplasia."

SUMMARY

A large family is described in which a high incidence of heart disease has been found (idiopathic cardiomegaly). Of a total of eighty-seven members so far considered (seventy-seven of whom have been examined, together with ten who are presumed to have died of the disease before the study commenced), thirty have been found to be affected.

A genealogic survey dating back to the arrival of the original immigrant from France in the early seventeenth century has allowed certain conclusions to be drawn with regard to hereditary characteristics. The pattern of occurrence over the five generations since the death (in 1860) of the man who is believed to have had the first case of heart disease in the family, clearly indicates a dominant non-sex-linked mode of transmission.

The diagnosis of heart disease in each case was based on the clinical findings and the electrocardiographic and radiologic changes. Two patients were asymptomatic and in these the only evidence for disease was electrocardiographic.

Dyspnoea on effort and syncopal attacks were the most common complaints. Sudden death occurred in eight instances. Frequent minor and major episodes of cerebral damage are considered to have resulted from emboli.

Significant abnormal physical findings were confined to the heart. Of the twenty patients with heart disease who were examined, rhythm was sinus in all but one. Nine had presystolic sounds, fifteen had systolic ejection murmurs, two had early diastolic murmurs, and six had mid-diastolic murmurs at the apex.

Electrocardiographic evidence of left ventricular hypertrophy or left bundle branch block was present in seven patients, but in most cases flat or diphasic T waves were the only abnormalities recorded. Cardiac enlargement was observed radiologically in fifteen patients and was predominantly left ventricular and left atrial. A frequent radiologic finding was an indentation seen in the left anterior oblique projection, identifying the junction of hypertrophied left ventricle and left atrium. The aortic shadow was considered to be abnormally small in eight patients.

Autopsies performed on three patients have revealed abnormalities restricted to the cardiovascular system. Hypertrophy and fibrosis of the myocardium, and hypoplasia of the aorta, have been constant findings. In addition, in two patients an unusual localized hypertrophy of the interventricular septum was found in which the hypertrophied myocardial fibres possessed a bizarre haphazard architectural arrangement. The cardiac valves and coronary arteries showed no disease.

The literature on idiopathic cardiomegaly and familial heart disease has been reviewed, and the various forms previously reported are compared with the disease observed in this family. In recent years an increasing number of reports on subaortic stenosis caused by asymmetrical hypertrophy of the interventricular septum indicate a growing awareness of this entity as a significant cardiac malformation. The observations on this family lend much support to previous contentions that the disease will frequently be familial, and it is hoped will stimulate further interest in the assessment of the relatives of subjects found to be affected.

Attempts have recently been made elsewhere to attack the hypertrophied septum surgically to relieve the subaortic stenosis. Insufficient time has elapsed to allow adequate assessment of the effectiveness of this procedure in prolonging life, but remedial surgery is being considered for the more severely affected members of the family under discussion, whose prognosis is, in any event, extremely poor.

The varied nomenclature that has been applied to this disease in the past, with both functional and organic connotations, has led to a confusion of terminology. The clinical and pathologic characteristics are now well delineated, but since the clinical findings are difficult to summarize in titular form, a descriptive term based on the pathologic anatomy appears desirable. "Hereditary cardiovascular dysplasia" is suggested as the most descriptive and least cumbersome name available.

Acknowledgment: A great amount of time and effort was expended by Dr. G. Germain of Coaticook, Quebec, and Dr. Y. Dandenault of Valleyfield, Quebec, in arranging for and encouraging the attendance of most of the members of the family at the laborious and occasionally tedious examining sessions that were required. Many of the family members are their patients, and their help and advice in this investigation is gratefully acknowledged.

ADDENDUM

Since our paper was submitted for publication, many articles [*44–53*] on familial cardiopathy have appeared in the literature.

CASE HISTORIES

CASE 1. *Jean B. (II).* This man died suddenly in his thirties. He had three brothers and four sisters, all of whom lived to at least fifty years of age, and none of whom were known to have suffered from heart disease. His father lived to the age of fifty or sixty years and apparently was not seriously ill during his lifetime. Jean B. was married in 1851 and died sometime in the early 1860's. This information was obtained from a ninety-five year old nephew.

CASE 2. *Jean B. (II).* This man, the only child of Jean B. (Case 1), died at the age of thirty-six, with a known history of heart disease. The last three weeks of his life were spent sitting in a chair because of orthopnoea. He had two daughters and three sons. One daughter died at the age of sixty-four in a mental institution; there is no information as to the state of her health or the cause of her death. The second daughter died at the age of seventy, and is known to have died with auricular fibrillation and a terminal episode of embolism to her lower extremities. One son died at the age of seventy from a cerebrovascular accident. The other two sons are (Cases 3 and 4) to be discussed. This information was obtained from his ninety-five year old cousin and from two daughters-in-law.

CASE 3. *Jos. B.* This man, son of Jean B. (Case 2), died suddenly at the age of thirty-seven while working on his farm. He had two children by each of two marriages, one child of each marriage died in infancy; cause of death was unknown. A son and daughter are still living. The case history on this man was obtained from his second wife.

CASE 4. *Alf. B.* This man, son of Jean B. (Case 2), died at the age of forty-six, two years after the onset of an illness described by his doctor as "dilated heart." For one and a half years before his death he was too disabled to work: he became more and more dyspneic before death and was unable to exert himself during the last year of his life. He never had swelling of the ankles and was never orthopneic. He became paralyzed on the day of his death. Of his thirteen children, one daughter has not been examined but is known to have heart disease and is forty-six years of age. Another daughter and son have been examined and were found to be free of disease. The other sons and daughters will be described as separate cases (Cases 5–12, 15 and 22). The information on Alf B. was obtained from his seventy-four year old wife who states that she had, in addition to her thirteen children, three miscarriages.

CASE 5. *Marie B.* This woman, daughter of Alf B. (Case 4), died at the age of forty-five, with a long history of heart disease. She had "dropsy" and required frequent paracenteses. She was very dyspneic and became paralyzed six months before death. She had two children, neither of whom have been examined. The information on this patient was obtained from her mother.

CASE 6. *Alire B.* This man, son of Alf B. (Case 4), died at the age of forty. Symptoms began at the age of thirty-two and consisted of severe cough and shortness of breath, which were recognized as being due to heart disease when he was thirty-six years of age. At that time he had a severe syncopal attack, and because of this and marked shortness of breath, he was advised to stop his work. During the last four years of his life he was an invalid, but did not show any orthopnoea or heart failure during most of this time. One year prior to death hemiparesis developed, and during the last six months of his life he was in heart failure. He died in 1949 but no autopsy was performed. However, a summary obtained from the

hospital in which he died described a diastolic murmur in the aortic area, and an electrocardiogram showed left axis deviation, prolonged P-R interval of 0.24 second, and QRS of 0.12 second. Of his ten children, one son has not yet been examined. Five daughters and two sons have been examined and have been found to be free from heart disease. One daughter and one son have been found to have heart disease, and will be discussed (Cases 19 and 20). The history of this man was obtained from his wife.

CASE 7. *Eva B.* (*Mrs. V. B.*) This woman, daughter of Alf B. (Case 4), died in 1943 at the age of thirty-three years. Disability dated from the age of eight years when she first complained of shortness of breath. During her married life she was always short of breath and required help to do her housework. She was never orthopneic and never manifested the signs of cardiac failure. Just prior to her death she suffered severe attacks of vomiting, and died suddenly following one of these attacks. She was not paralyzed. No autopsy was performed. Of her two children, one son was examined and found to be free from heart disease. Her daughter will be described (Case 14). In addition to the two living children, this woman had three miscarriages. The case history was obtained from her husband and her mother.

CASE 8. *Gerard B.* This man, son of Alf B. (Case 4) died in 1956 at the age of forty-three years. He worked as a delivery man for a bakery and was accustomed to climbing fifty sets of stairs each morning without disability until the Winter of 1956. At that time he became weak, a cough developed, and he had digestive upsets. In the Summer of 1956 a severe pain developed in the chest which lasted for three days and which was followed by haemoptysis. Following this episode he was confined to bed with cough, dyspnoea, orthopnoea and fatigue. On the day prior to his death a severe headache developed which was followed by a left-sided paralysis and aphasia. An electrocardiogram showed wide notched P waves (0.14 second) with sinus rhythm and right bundle branch block. Of three daughters, two were found to be normal on examination; the third will be described (Case 21). The history on this man was obtained from his wife.

CASE 9. *Albert B.* This man, son of Alf B. (Case 4), died at the age of thirty-five years, his history dating from the age of eighteen years at which time a temporary episode of aphasia and paralysis developed. He recovered completely from this episode and remained well for the next three years. At the age of twenty he was turned down for military service because of his heart. Dyspnoea was troublesome for six years prior to his death, but he was never orthopneic. He complained a great deal of digestive trouble with gaseous eructations, and had transitory attacks of weakness or "blackouts" which, however, did not go on to syncope. During the last four months of his life these "blackouts" became so disabling that he had to give up his work. He died suddenly one day while working in his garden and was observed to have frothy expectoration terminally. Of his five children, two boys and one girl were found to be normal on examination. Two other boys have been found to have heart disease and will be described (Cases 29 and 30). The information on this man was obtained from his wife.

CASE 10. *Therese B.* This girl, daughter of Alf B. (Case 4), died suddenly at the age of twelve years on her way to church. She had complained of dyspnoea for about five to six months before death. On the morning of her death she appeared to be in good health when she left home, but asked her older sister to slow up because she was walking too fast. Suddenly she said, "I see everything black," and fell down and died immediately. There was no history of orthopnoea, syncope, cardiac failure or paralysis. Her case history was obtained from her mother and from the sister who was present at the time of her death.

CASE 11. *Wilfred B.* This man, son of Alf B. (Case 4), had no symptoms until the age of thirty-six when he noticed dyspnoea and some pressure in the chest while on a hunting trip. These symptoms did not increase and were not accompanied by orthopnoea or palpitations. He was admitted to a hospital three years later in September 1957, with complaints of numbness in the right side of the face and right arm. He showed no evidence of cardiac failure when first seen, but his heart was moderately enlarged on clinical examination. He had an atrial sound, a normal first sound, and a widely split second sound. There were no murmurs. The blood pressure was 120/80 mm. Hg. By radiologic examination all chambers of the heart were enlarged, predominantly the left ventricle. A prominent notch was observed at the left atrioventricular junction as seen in the left anterior oblique projection, compatible with hypertrophy of these two chambers. The aortic knob was small. There was evidence of pulmonary venous congestion. The electrocardiogram showed a normal sinus rhythm with occasional ventricular extrasystoles. The P waves were notched and slurred. The QRS complexes were those of an incomplete left bundle branch block. The urinalysis was normal. His haemoglobin was 100 per cent. The white blood count was 7,000 per cu. mm. with a normal differential. Roentgenograms of the skull, blood sugar, blood Wassermann test, serum non-protein nitrogen, electroencephalogram and cerebrospinal fluid examinations were all normal. Serum cholesterol was 110 mg. per cent (normal values 150 to 250 mg. per cent), total lipids 515 mg. per cent. The patient was given anticoagulants for the demonstrated cerebral vascular disease and was discharged to the care of his own doctor. Subsequently several cerebral

vascular accidents developed with right-sided hemiplegia and aphasia, and he was confined to bed at home where he died in May 1959. During the last few months of his life cardiac failure developed and he was treated with digitalis and diuretics. Permission for autopsy was obtained. This man had three sons and one daughter, of whom two sons were considered to have normal hearts. One son and the daughter will be discussed (Cases 27 and 28).

At autopsy the heart (680 gm.) was found to be enlarged, with dilatation of all chambers. The myocardium of the right ventricle was normal; that of the left was thickened, measuring 10 mm. at the apex and 14 mm. at its mid-portion. The interventricular septum was of normal width and did not contain a localized hypertrophied muscle mass. Multiple areas of fibrosis were seen scattered throughout the interventricular septum and left ventricle, particularly on their anterior aspects where the endocardium was thickened and a mural thrombus was firmly attached.

On microscopic examination the muscle fibres were hypertrophied and showed some disintegration with replacement by connective tissue. The architectural pattern did not appear to be unusual. The aorta was narrowed and was 2.4 cm. in diameter, 5.2 cm. in circumference, and 2 mm. in thickness above the aortic valve. At the arch of the aorta the measurements were, respectively, 2.3 cm., 4.8 cm. and 2 mm. There was slight thickening of the middle leaflet of the mitral valve, but no stenosis, and the other valves were all normal. The coronary arteries were patent throughout. There was hypoplasia of the muscle coat of the aorta and there was a moderate degree of arteriosclerosis. Evidence of old and recent infarcts were found in the lungs, the kidneys, the brain and the intestines.

Case 12. *Rene B.* This man, son of Alf. B. (Case 4), had no symptoms except for vague epigastric discomfort until July 1957, when he had severe retrosternal pain which confined him to bed for a week. At the end of that time he felt well enough to return to work. About one month after the pain he had a severe grand mal seizure and left hemiplegia developed for which he was admitted to the hospital in August 1957, at the age of forty-one. On examination at that time, in addition to his left paresis, he was orthopneic and had Cheyne-Stokes breathing. His blood pressure was 98/50 mm. Hg and the heart showed sinus rhythm at the rate of 80. His heart was not reported as clinically enlarged but he had a widely split second sound at the base and an early diastolic murmur. Radiologically, cardiac enlargement was slight to moderate in degree and was predominantly left ventricular. The aorta was small. There was a considerable degree of pulmonary vascular congestion. The electrocardiogram showed sinus rhythm with ventricular extrasystoles, some of them in runs of bigeminy. The P wave was wide and notched. The QRS complexes were abnormal, being widely splintered in the pattern of non-specific intraventricular block. The QRS was 0.12 second wide in lead aVL.

On admission, the urine showed albumin and pus cells which disappeared after treatment for cystitis. The haemoglobin was 86 per cent, and the white blood count, initially 21,000 per cu. mm. with neutrophilia, fell to 9,000 per cu. mm. at the time of discharge. Roentgenograms of the skull, blood sugar, blood Wassermann test and serum non-protein nitrogen were within normal limits. Serum cholesterol was 104 mg. per cent. During his hopsital stay he recovered some strength in his left leg and was discharged home where he lived for one year. He was mildly dyspneic until a few days before his death when he became acutely dyspneic and had several attacks of pulmonary oedema. He died in December 1958, two and a half years after the onset of symptoms. No autopsy was performed. His only two children will be described (Cases 13 and 26).

Case 13. *Claude B.* This boy, son of Rene B (Case 12), had symptoms of heart disease from infancy, when he would smother in his crying and become blue. He had shortness of breath all his life, which prevented him from engaging in any strenuous sports, although he was able to go to school. He never had orthopnoea, cough or palpitations. On two occasions he suddenly lost consciousness while exerting himself and was reported to have been unconscious for ten minutes. A doctor discovered a heart murmur when he was seven years old. On examination he was a well developed boy of eighteen, looking healthy. The abnormal findings were confined to the cardiovascular system. He had a forceful apical impulse which was bifid or reduplicated in character. The first sound was widely split. He had a grade 3/6 pansystolic murmur and a short, faint middiastolic murmur, heard best at the apex. The blood pressure was 110/40 mm. Hg. Radiologically, he had an increased ventricular mass, thought to represent both right and left ventricular hypertrophy, a moderately enlarged left atrium, and a prominent notch at the left atrioventricular groove. The main pulmonary artery was slightly enlarged but there was no pulmonary venous congestion. The aorta was small. The electrocardiogram showed tall and pointed P waves in leads II, III and aVF. The QRS complexes were of a high voltage in a pattern of left bundle branch block. He died suddenly in January 1959, at the age of eighteen.

Postmortem examination revealed a heart which was moderately enlarged and weighed 575 gm. There was myocardial hypertrophy involving all chambers but especially the left ventricle. The thickness of the left ventricle varied from 12 mm. at the apex to 20 mm. at the mid-portion. There was a localized nodular hypertrophy of the cephalic two-thirds of the inter-

ventricular septum which measured 32 mm. in thickness. This mass bulged into the right ventricle, distorting its outlines, narrowing the lumen and producing a globular shape to the heart. It also bulged, to a lesser extent, into the left ventricle, narrowing the outlet. The aorta looked small and narrow and measured 2 cm. in diameter and 2 mm. in thickness 1 cm. above the aortic valve. At the aortic arch the diameter was 2 cm. and the thickness 1 mm. The coronary arteries, the valves of the heart and the endocardium were all within normal limits.

On microscopic examination the myocardial fibres were hypertrophied and there was a peculiar haphazard architectural arrangement. In addition to this bizarre distribution of muscle fibres there was also some disintegration of the cytoplasm. Multiple and irregular areas of scarring were found scattered in the myocardium of both ventricles and interventricular septum. Microscopic examination also revealed the aorta and the medium-sized arteries to have thin walls with hypoplastic muscle coat containing some basophilic mucoid substance.

CASE 14. *Noella B.* This twenty year old girl, daughter of Eva B. (Case 7), died suddenly in church in February 1959. Her history was similar to that of her mother (Case 7). From the age of six years she was subjected to attacks of shortness of breath and weakness, accompanied by coughing and sweating, about once a month. A doctor who saw her then said that she had heart disease. The severe attacks disappeared at the age of eight years but she continued to have weakness and pain in the legs. Her dyspnoea was such that she could scarcely walk on the flat without becoming short of breath, but she never had orthopnoea, syncopal attacks or swollen ankles. On physical examination she was well developed, and abnormal findings were confined to the cardiovascular system. She had a widespread systolic murmur, 3/6. Her blood pressure was 120/76 mm. Hg. Roentgenographic examination showed enlargement of both ventricles and the left atrium. She had a prominent notch at the left atrioventricular junction. The aorta was small. The electrocardiogram showed diphasic P waves in leads V_1 and V_2 and abnormal notching of the QRS complexes, the QRS being 0.09 second wide. The T waves in leads V_6 and V_7 were flat.

A postmortem examination was performed on the embalmed body of this patient and the organs were in a rather poor state of preservation. The heart weighed 505 gm. There was mild hypertrophy of both atria, moderate hypertrophy of the right ventricle, which was 5 mm. thick, and marked hypertrophy of the left ventricle and interventricular septum in its cephalic two-thirds. The left ventricle measured 20 mm. in its mid-portion and 8 mm. at the apex. The interventricular septum was 30 mm. thick at the level of the nodular thickening. The localized hypertrophy of the interventricular septum protruded into the lumens of both ventricles, narrowing their outlets and distorting the shape of the heart. The aorta appeared narrowed and was 2.4 cm. in diameter above the aortic valve and 2 mm. in thickness in this area. At the arch of the aorta the measurements were 2.6 cm. for the diameter and 2 mm. for the thickness of the aortic wall. The valves of the heart, although somewhat destroyed by the process of embalming, were considered to be normal. There was no evidence of any disease of the coronary arteries. The endocardium of all heart chambers was smooth and transparent. Microscopically, there was marked hypertrophy of the muscle fibres and a bizarre distribution of these fibres which seemed to lack organization. Disintegration of muscle fibres was also present. Multiple areas of scarring were noted throughout the myocardium. The muscle coats of the aorta and the medium-sized arteries were hypoplastic and showed an accumulation of slightly basophilic and mucoid substance between thinned muscle fibres.

CASE 15. *Lauza (Mrs. L. G.)* This fifty year old woman, daughter of Alf. B. (Case 4), had few symptoms and was able to perform all her housework without difficulty, but she believed she was weaker and had more dyspnoea than other women of her age. On examination she appeared to be healthy. Her blood pressure was 140/80 mm. Hg; her heart was in sinus rhythm at a rate of 84 per minute. Her heart sounds were normal with the addition of a low-pitched atrial gallop. Roentgenographic examination of the chest was normal. The electrocardiogram was abnormal, showing slightly depressed S-T segments from leads V_4 to V_6 with diphasic T waves. Of her four children, two boys were believed to be free of heart disease; one boy and a girl had abnormal hearts and will be described (Cases 16 and 17).

CASE 16. *Andre G.* This boy, son of Lauza (Case 15), had no symptoms. On examination his blood pressure was 125/80 mm. Hg. He had a grade 1 systolic murmur. A roentgenogram of the chest was normal. An electrocardiogram showed right bundle branch block pattern.

CASE 17. *Jeannine G.* This eighteen year old girl, daughter of Lauza (Case 15), was found to have a heart murmur as an infant, and had symptoms of heart disease. As a child she had fainting attacks, fatigue, palpitations, dyspnoea and cough on the slightest exertion. On physical examination her heart was enlarged and fibrillating. She had a loud split first sound at the apex with a pansystolic murmur. After exercise she had an opening snap and a mid-diastolic murmur. Her blood pressure was 110/70 mm. Hg. She had an atrial fibrillation. On radiologic examination all cardiac chambers were considered enlarged, and there was considerable pulmonary

vascular congestion. The electrocardiogram showed auricular fibrillation with abnormal notching of the QRS complexes which were 0.09 second wide, and negative T waves in leads aVF and V_5 to V_7. A tracing made just before death showed complete atrioventricular block. Death occurred following a brief period of heart failure. Autopsy was not performed.

CASE 18. *Lise B.* This eighteen year old girl, daughter of Joseph B. (Case 22), had no symptoms except frequent nosebleeds and a story of her legs becoming red and blue after standing for any length of time. The physical examination was within normal limits. Her blood pressure was 120/80 mm. Hg. A roentgenogram of the chest was normal. The electrocardiogram showed only a non-specific intraventricular conduction defect and a Q in lead aVF 9 mm. with an R of 23 mm.

CASE 19. *Lucille B.* This twelve year old girl, daughter of Alire B. (Case 6), was active and had no symptoms. An atrial and a third heart sound were heard. Radiologically, there was slight enlargement of both ventricles and of the left atrium. The electrocardiogram was abnormal in that it showed inverted T waves in leads aVF and V_5 to V_7.

CASE 20. *Henri B.* This eleven year old boy, son of Alire B. (Case 6), had no symptoms until the age of ten years, when he noticed unusual dyspnoea and weakness on taking part in active sports. On examination he had a grade 3/6 rough mid-systolic murmur heard over the entire precordium, and a third heart sound which was elicited by exercise. The blood pressure was 130/85 mm. Hg. Radiologic examination revealed slight enlargement of both right and left ventricles. A left atrioventricular notch was present posteriorly, and the size of the aorta was at the lower limits of normal. The electrocardiogram showed S-T depression in leads V_2 to V_5 and negative T waves in leads I, aVL and V_5 to V_7.

CASE 21. *Jacinthe B.* This twelve year old girl, daughter of Gerald B. (Case 8), had shortness of breath and weakness on slight exertion since the age of six years, at times severe enough to keep her in bed. She had pain in her legs, particularly in bed at night. On examination she was pale, but well developed and well nourished. She had an atrial sound, a high-pitched mid-systolic murmur grade 2/6, and a mid-diastolic murmur heard at the apex. Her blood pressure was 105/65 mm. Hg. Radiologically, there was enlargement of all cardiac chambers, graded as slight to moderate in degree. The aorta was small. A second roentgenogram taken a year later showed an increase in cardiac size during that interval. An electrocardiogram was abnormal, showing biphasic T waves in leads II, III and aVF and inverted T waves in leads V_4 to V_7. The serum cholesterol level was 112 mg. per cent.

CASE 22. *Joseph B.* This forty-four year old man, son of Alf. B. (Case 4), had no symptoms other than complaints of poor digestion and frequent nosebleeds. On examination he was well developed; a faint atrial sound and a systolic murmur grade 2/6 were heard. The blood pressure was 135/85 mm. Hg. A roentgenogram of the chest was within normal limits. The electrocardiogram was abnormal, showing negative T waves in leads I, II and V_5 to V_7. His serum cholesterol level was 212 mg. per cent. Of his six children, one girl and one boy were believed to be free of heart disease. Three girls and one boy will be discussed (Cases 18, 23, 24 and 25).

CASE 23. *Marcelle B.* This seventeen year old girl, daughter of Joseph B. (Case 22), had dyspnoea on exertion. On physical examination she was a plump, well developed girl. Her heart was not clinically enlarged, but she had an apical third sound heard after exercise. Her blood pressure was 124/80 mm. Hg. Radiologic examination showed slight enlargement of the right and left ventricles and of the left atrium, with an indentation marking the junction of the left atrium and the left ventricle. The electrocardiogram was abnormal, with a QS pattern in leads V_2 and V_3 and negative T waves in leads II, aVF and V_5 to V_7. The serum cholesterol level was 171 mg. per cent.

CASE 24. *Gisele B.* This fifteen year old girl, daughter of Joseph B. (Case 22), had no symptoms and was active in sports. On examination she had only a faint mid-systolic murmur, heard best at the apex, and a third heart sound heard after exercise. The blood pressure was 120/75 mm. Hg. Radiologically, there was a slight to moderate enlargement of both ventricles and of the left atrium, with left atrioventricular notching posteriorly. The electrocardiogram was abnormal, showing a negative T in leads II, III, aVF and V_4 to V_6. The serum cholesterol level was 204 mg. per cent.

CASE 25. *Yves B.* This eleven year old boy, son of Joseph B. (Case 22), had had weakness and dyspnoea on exertion since the age of two years. He was thin and slightly pigeon breasted. He had a grade 2/6 apical systolic murmur and a loud third heart sound heard at the apex. His blood pressure was 120/70 mm. Hg. Roentgenographic examination of the chest showed slight but definite enlargement of the left atrium and possible enlargement of the left and right ventricles. The electrocardiogram was within normal limits. The serum cholesterol level was 141 mg. per cent.

CASE 26. *Leo B.* This sixteen year old boy, son of Rene B. (Case 12), had been quite well until one year previously when he first noted shortness of breath while playing hockey. At about the same time he had an acute febrile illness and a syncopal attack. He did not complain of orthopnoea or weakness. On examina-

tion he was a muscular young man. He had a systolic thrill, an atrial sound, a 4/6 mid-systolic murmur and a short mid-diastolic murmur. Radiological examination performed in 1958 and repeated in 1959 showed enlargement of both ventricles and atria, with a slight increase in the heart size during the year. He had prominent notching at the junction of the left atrium and ventricle. The aorta was small. The electrocardiogram was abnormal, showing diphasic P waves in leads V_3R to V_3, high voltage QRS complexes, abnormal Q waves in leads aVF and V_5 to V_7. He was admitted to the Royal Victoria Hospital for further investigation in April 1959. Urinalysis, protein electrophoresis, serum electrolytes, blood sugar, cardiac output at rest and with exercise, and blood volume were all found to be within normal limits. His white blood count was 13,400 per cu. mm. with slight leukocytosis and eosinophilia. He had slightly reduced prothrombin activity. His blood group was O positive. Skin tests for toxoplasmosis, histoplasmosis and tuberculosis were negative. A tomogram of the lungs revealed normal vasculature. Pulmonary function tests showed normal ventilation, diffusion, arterial blood oxygen and carbon dioxide. A roentgenogram of the skull and an electroencephalogram were within normal limits. The serum cholesterol level was 153 mg. per cent.

Case 27. *Denis B.* This fourteen year old boy, son of Wilfred B. (Case 11), was asymptomatic until the age of ten years when he had an isolated syncopal attack. At about thirteen years he started noticing shortness of breath on exertion, first while playing actively, later on with only moderate activity. He had no orthopnoea. On examination he had a grade 1/6 systolic murmur. Roentgenographic examination of the chest revealed no abnormalities. The electrocardiogram was abnormal, showing an inverted T wave in leads aVF and V_4 to V_6.

Case 28. *Claire B.* This eighteen year old girl, daughter of Wilfred B. (Case 11), had only vague symptoms of dyspnoea when first seen in 1958, but by 1959 not only had dyspnoea developed while walking on the level but also orthopnea and oedema of the ankles. She had a dry cough. On physical examination she was well developed. There was a mid-systolic murmur along the left sternal border and a third heart sound heard after exercise. Roentgenographic examination of the chest was within normal limits in 1958 but in 1959 showed slight but definite enlargement of all cardiac chambers. The electrocardiogram was abnormal, with inverted T waves in leads aVF and V_5 to V_7.

Case 29. *Luc B.* This sixteen year old boy, son of Albert B. (Case 9), was found to have a heart murmur at the age of three years when he was admitted to the hospital for investigation of repeated epistaxes. He had never been strong and suffered continuously from a dry cough, shortness of breath on exertion, and blackouts or giddiness on unusual straining. At the age of thirteen years he became orthopneic after a severe infection of the lower respiratory tract and was admitted to another hospital for investigation. He was reported to have had an elevated pulmonary artery and capillary pressure on cardiac catheterization. On physical examination he was muscular and well developed. He had a 3/6 mid-systolic murmur at the apex and a third heart sound accompanied by a short mid-diastolic murmur at the apex. The blood pressure was 120/60 mm. Hg. Radiological examination in 1958 showed only a slight enlargement of all chambers, with an indentation between the left atrium and ventricle. By 1959 further enlargement had occurred, particularly of the ventricles. The aorta was smaller than normal. His electrocardiogram was abnormal, with tall or notched P waves (4 mm. in lead II), a Q wave in leads aVL 0.04 seconds wide and 8 mm. tall (R 14 mm.). T waves were negative in leads I, aVL and V_5 to V_7. A more complete investigation was carried out at the Royal Victoria Hospital and showed a low cardiac output of 3.3 L./min. at rest, with an increase of only 0.6 L. on exercise. Vital capacity and functional residual capacity were slightly decreased. Pressure-volume studies revealed normal lung mechanics. Arterial oxygen saturation and carbon dioxide were normal. An electroencephalogram showed a paroxysmal dysrhythmia seen maximally in the temporal posterior and central head regions. Roentgenograms of the skull were within normal limits. Prothrombin activity was slightly decreased. The serum cholesterol level was 96 mg. per cent, well below the normal range of 150 to 250 mg. per cent. White blood count, differential, haemoglobin and red cells were all within the normal range, as were protein electrophoresis, serum electrolytes, blood sugar, urinalysis and blood volume.

Case 30. *Roch B.* This fourteen year old boy, son of Albert B. (Case 9), was said by his mother to have been short of breath since the age of six or seven. At the time we saw him he was unable to play hockey for long without becoming acutely dyspneic. He had had one transitory syncopal attack, but suffered repeated attacks of dizzy spells on exertion. On examination he was pale but of stocky build. He had a bifid apical impulse and an apical systolic thrill. The heart sounds were normal, with an atrial sound, a 4/6 systolic murmur heard maximally along the left sternal border, and a third heart sound accompanied by a short mid-diastolic murmur at the apex. The electrocardiogram was abnormal, showing high voltages of the QRS complexes, the R wave 50 mm. and the S wave 60 mm. in lead V_3R. He had S-T depression in leads I, aVL, V_4 to V_7 and negative T waves in the same leads. Roentgenographic examination of the chest in 1958 showed slight enlargement of all cardiac chambers, which had

increased on a repeat examination in 1959. A left atrioventricular notch was present posteriorly, and the aortic size was small. He was admitted to the Royal Victoria Hospital for further investigation. Serum protein, electrophoresis, electrolytes, blood sugar, Wassermann test, urinalysis, electroencephalogram, skin tests for toxoplasmosis, histoplasmosis and tuberculosis, tomography of the lungs and roentgenograms of the skull were all normal. He had a normal cardiac output and blood volume. Prothrombin activity was slightly decreased. The serum cholesterol level was 106 mg. per cent. Results of pulmonary function tests were normal, except for a slight decrease in the vital capacity and the functional residual capacity.

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Congenital Aortic Regurgitation*

Clinical and Hemodynamic Findings in Four Patients

CHARLES J. FRAHM, M.D.,† EUGENE BRAUNWALD, M.D. *and* ANDREW G. MORROW, M.D.
Bethesda, Maryland

CONGENITAL aortic regurgitation is commonly found in association with other congenital cardiovascular malformations, such as valvular or subvalvular aortic stenosis [*1*], coarctation of the aorta [*2*], ventricular septal defect [*3*] and absence of the pulmonic valve [*4*]. Isolated congenital aortic regurgitation, on the other hand, is an entity which has not been clearly established. Many of the standard textbooks [*4–13*] make no mention of this malformation; others [*14–16*] have suggested that it may exist but no detailed clinical or hemodynamic observations have been published. We have recently had the opportunity to study four patients with isolated, congenital aortic regurgitation, and descriptions of the clinical and hemodynamic findings in them form the basis of this report.

CASE REPORTS

CASE I. In G. P. (02-57-94), a six year old Polynesian boy, a heart murmur was detected during the first week of life. His growth and development had been somewhat slow in comparison to his siblings. There was no history of rheumatic fever or of its stigmata, and there were no symptoms referable to the cardiovascular system. On examination he appeared to be small for his age. He had bounding arterial pulses and the arterial pressure in the arms was 120/60/0. The point of maximum impulse was in the fourth intercostal space at the mid-clavicular line, and there was a moderate left ventricular lift. A grade 4/6 long, blowing, diastolic murmur was heard over the entire precordium but was most prominent at the second right intercostal space. A short, grade 1/6 ejection murmur was heard best along the left sternal border and an aortic ejection sound was audible over the entire precordium. (Fig. 1.) Due to the intensity of the diastolic murmur, splitting of the heart sounds at the base could not be determined accurately by auscultation, but the phonocardiogram revealed the second heart sound to be widely split.

The chest roentgenogram showed that there was a definite increase in the transverse cardiac diameter with evidence of left atrial and ventricular enlargement. (Fig. 2.) The thoracic aorta was dilated and pulsated vigorously; the electrocardiogram revealed left axis deviation and left ventricular hypertrophy. (Fig. 3.) Cardiac catheterization revealed that the pressures in the right atrium, right ventricle and pulmonary artery were normal, and the nitrous oxide test indicated that there were no cardiac shunts [*17*]. In order to assess the functional status of the aortic valve, a retrograde left ventricular catheterization was performed [*18*]; there was no systolic pressure gradient across the aortic valve, but the pressure in the central aorta (80/32 mm. Hg) was consistent with moderate aortic regurgitation. (Fig. 4.) The thoracic aortogram (Fig. 5) revealed reflux of the contrast substance from the aorta into a dilated left ventricle; the aortic cusps were not well visualized. When re-examined one year after these studies the patient was still asymptomatic and the clinical findings were unchanged.

CASE II. A. D. (01-32-89), a seventeen year old white boy, had been told of a heart murmur at the time of his first detailed physical examination at the age of sixteen years. He had no cardiac symptoms or history suggestive of rheumatic fever or syphilis. On examination the pulses were hyperactive and the blood pressure was 105/50 mm. Hg. The heart was not enlarged and there were no abnormal lifts or thrills. The second heart sound in the aortic area was accentuated and louder than in the pulmonic area. A grade 3/6 blowing, diastolic murmur was most clearly audible along the left sternal border at the third and fourth intercostal spaces. A grade 2/6 harsh ejection systolic murmur was present in the same area and was also transmitted into the neck.

Roentgenographic examination of the chest showed no abnormality of the heart (Fig. 6), but there was some prominence of the ascending aorta and aortic arch. The electrocardiogram indicated the presence of an intraventricular conduction defect with a QRS duration of 0.11 second and suggested left ventricular hypertrophy. (Fig. 3.) The pressures in the chambers

* From the Clinic of Surgery, National Heart Institute, Bethesda, Maryland.
† Present address: Chicago, Illinois.

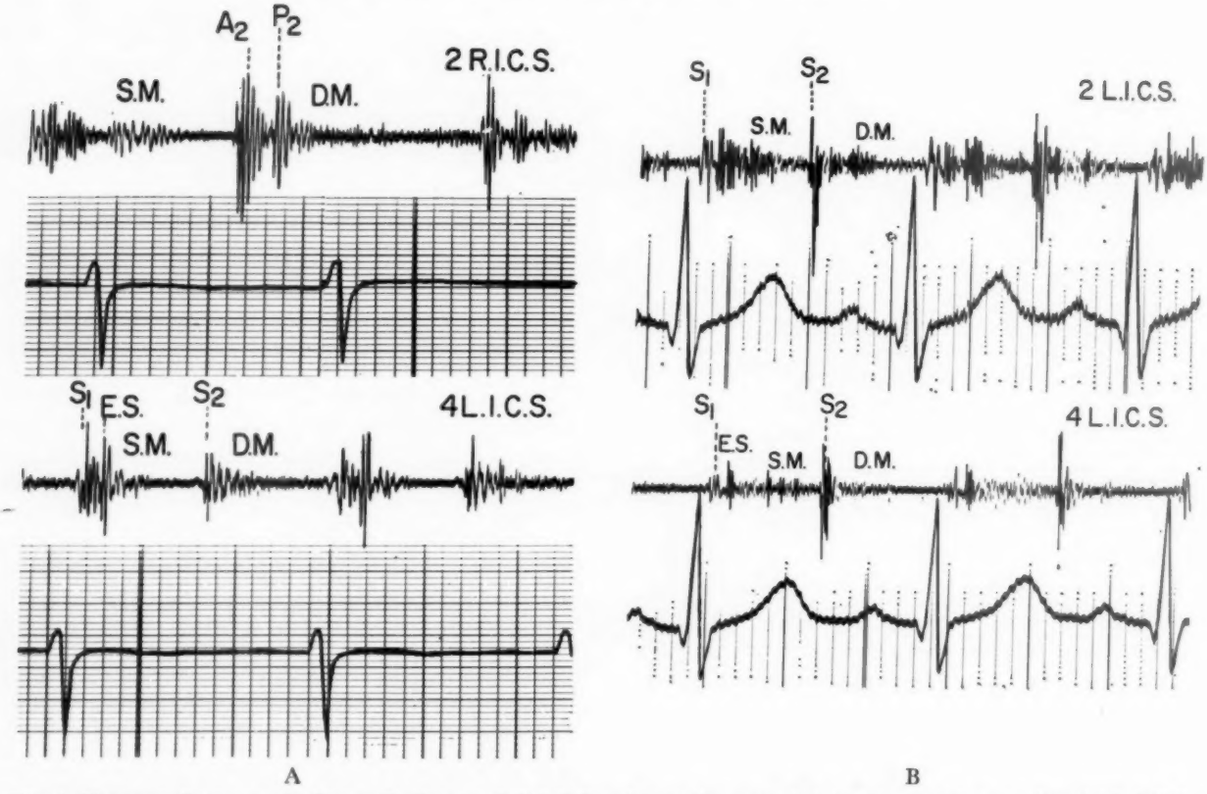

FIG. 1. Phonocardiograms. A, Case I. B, Case III. 2 R.I.C.S. refers to the second right intercostal space. 2 and 4 L.I.C.S. refer to the second and fourth left intercostal spaces, respectively. S_1 and S_2 refer to the first and second heart sounds. S.M. = systolic murmur; D.M. = diastolic murmur; A_2 = aortic valve closure sound; P_2 = pulmonic valve closure sound; E.S. = ejection sound.

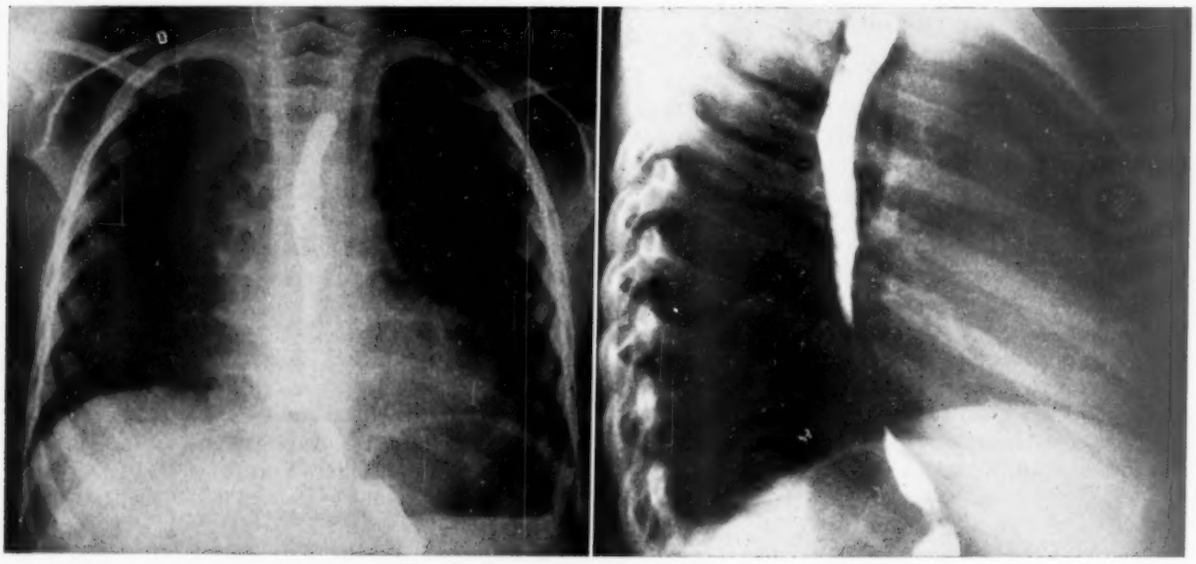

FIG. 2. Case I. Chest roentgenograms.

of the right side of the heart and pulmonary artery were normal and there were no circulatory shunts. The thoracic aortogram showed reflux of dye into the left ventricle, and only two aortic sinuses of Valsalva were present. The left carotid and the left subclavian arteries were considered to be separated by an abnormal distance and the aortic arch bent acutely. (Fig. 7.)

The patient remained well and when re-examined four years after the studies described there was no

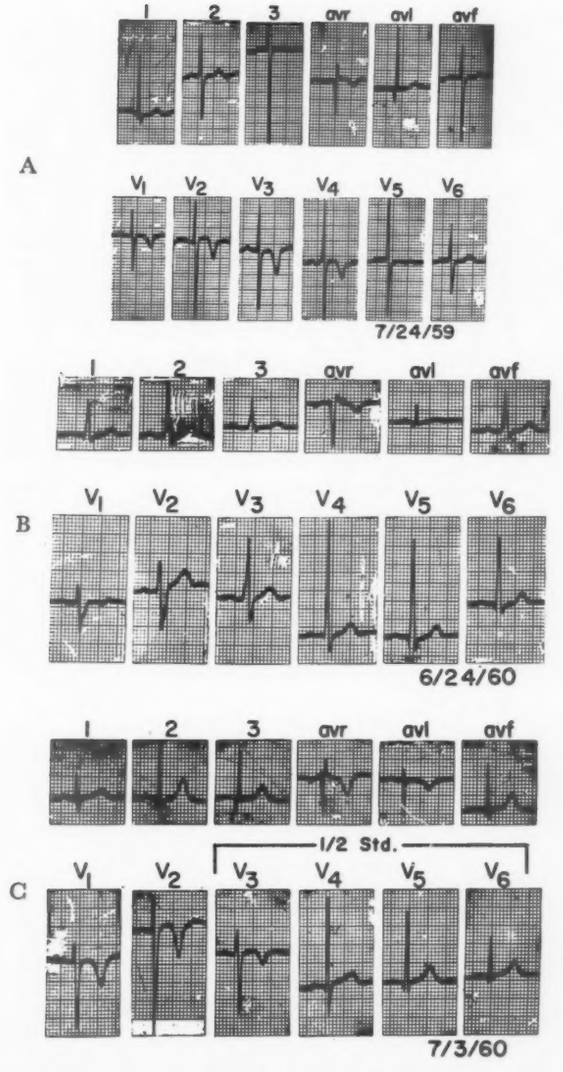

FIG. 3. Electrocardiograms. A, Case I. B, Case II. C, Case III.

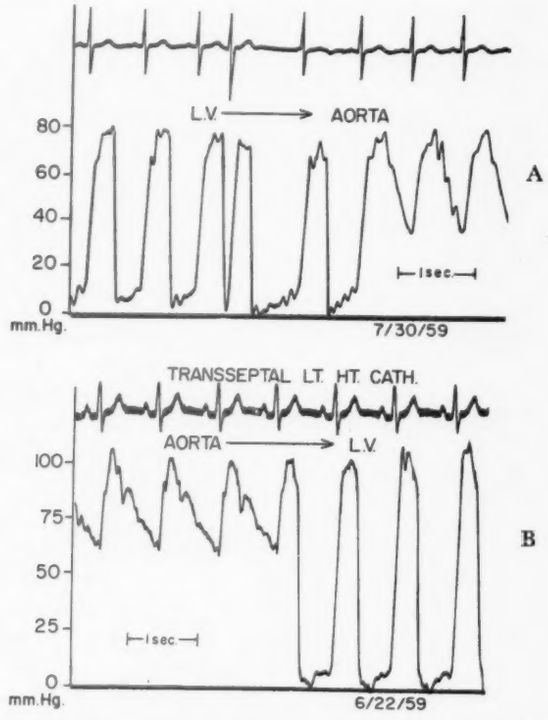

FIG. 4. Pressure tracings obtained from the left ventricle (LV) and aorta as the catheter was pulled across the aortic valve. A, Case I. B, Case II.

change in the physical findings. A transseptal left heart catheterization [*19*] carried out at this time revealed normal pressures in the left atrium and left ventricle and no pressure gradients across the mitral or aortic valves. (Fig. 4.)

CASE III. In R. S. (03-07-18), a seven year old boy, a heart murmur had been detected at the age of six weeks. There were no symptoms except for minimal fatigue after exertion; there was no history of rheumatic fever. He had been considered to have a patent ductus arteriosus, but cardiac catheterization at another hospital failed to support this diagnosis and he was referred to the National Heart Institute for further studies. On examination the peripheral pulses were brisk, the blood pressure was 108/58 mm. Hg, and there was a prominent left ventricular lift. Auscultation revealed a prominent ejection sound at the base and a third heart sound at the apex. A grade 3/6 to and fro (systolic-diastolic) murmur was best heard in the second and third intercostal spaces at the left sternal border. On auscultation all observers considered the murmur to be continuous, but on the phonocardiogram it was seen not to peak at the time of the second sound and the tracing was more suggestive of two distinct murmurs. (Fig. 1.)

The chest roentgenogram showed that the transverse diameter of the heart was slightly increased and there was definite convexity of the left border. (Fig. 8.) The ascending aorta was dilated and pulsated vigorously. The electrocardiogram displayed left ventricular hypertrophy. (Fig. 3.) Right heart catheterization revealed normal pressures in the pulmonary artery and the right side of the heart and no cardiac shunts. At transseptal left heart catheterization the pressures in the left atrium were normal and there was no systolic pressure gradient across the aortic valve. (Fig. 9.) The central aortic pressure (105/50 mm. Hg) was compatible with the diagnosis of aortic regurgitation. In order to estimate the severity of the aortic regurgitation, cardio green dye was injected into the thoracic aorta and its appearance detected in the right ear. [*20*]. This study showed that dye injected into the aorta as low as the eleventh thoracic vertebra immediately refluxed to the origin of the innominate artery, indicating the presence of moderately severe aortic regurgitation.

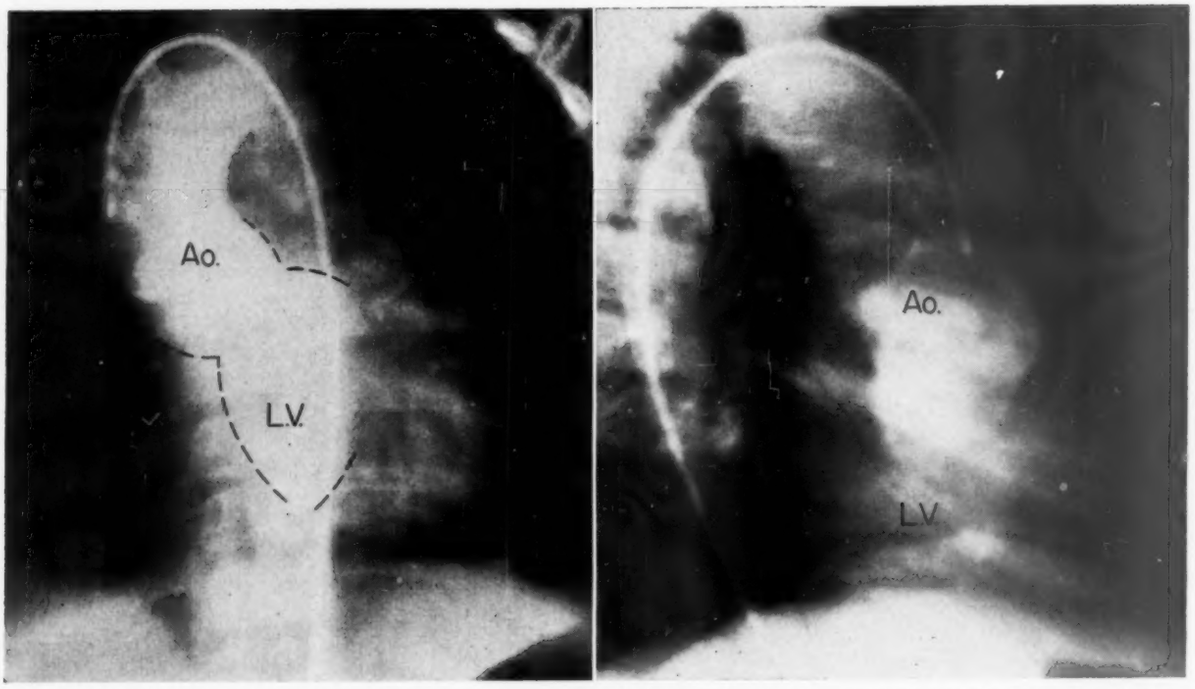

FIG. 5. Case I. Retrograde thoracic aortogram. The anteroposterior projection is on the left and the lateral projection on the right. Ao = aorta; LV = left ventricle.

FIG. 6. Case II. Chest roentgenograms.

CASE IV. In G. M. (03-20-68), a twenty-nine year old white man, a cardiac murmur was discovered for the first time at the age of eight years. He had noted excessive fatigability all of his life but he gave no history of rheumatic fever or any of its manifestations. Four years prior to admission he began to experience sharp anterior chest pain associated with physical exertion but not otherwise typical of angina pectoris; he had no symptoms of diminished cardiac reserve. On physical examination the blood pressure in the right arm was 135/80 mm. Hg and the jugular venous pulse was normal. A left ventricular lift was felt just outside the mid-clavicular line, and auscultation at the apex revealed a faint first heart sound followed by a loud aortic ejection sound. Along the left sternal border there was a grade 3/6 ejection systolic murmur and a grade 2/6 blowing diastolic murmur.

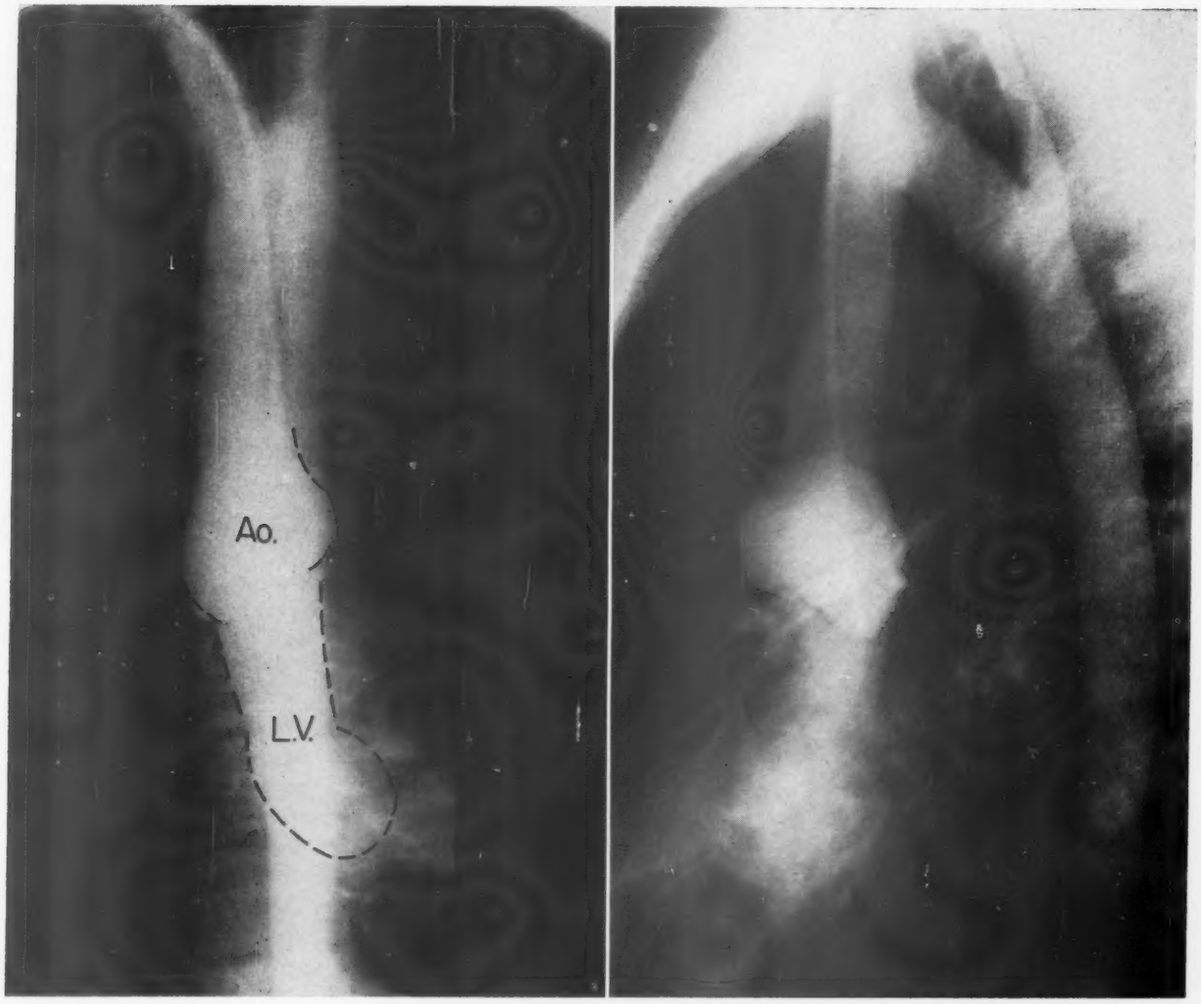

FIG. 7. Case II. Retrograde thoracic aortogram. The anteroposterior projection is on the left and the lateral projection is on the right. Ao = aorta; LV = left ventricle. In the lateral view the sharp angulation of the aortic arch, frequently observed in patients with coarctation of the aorta is present.

Chest roentgenograms revealed the heart to be moderately enlarged in its transverse diameter, with prominence of the left ventricle; the aorta bulged to the right and on fluoroscopy it pulsated vigorously. No valvular calcification was seen. The electrocardiogram was within normal limits. Cardiac catheterization revealed normal pressures in the right side of the heart and in the pulmonary artery; there were no cardiac shunts [*17*]. Transseptal left heart catheterization showed normal pressures in the left atrium and ventricle, and no gradient across either the aortic or mitral valves. To determine the degree of aortic regurgitation a retrograde aortic catheterization was performed [*20*]. The pressures in the central aorta were 87/49 and indicator dye regurgitated from a point 2 cm. below the aortic arch back to the origin of the innominate artery; this test was interpreted to indicate that a slight degree of aortic regurgitation was present.

COMMENTS

As already indicated, isolated congenital aortic regurgitation has been considered to be extremely rare and the clinical and hemodynamic features of this malformation have not been described previously. Harvey [*15*] has indicated that in only two of his 600 patients with aortic regurgitation was the lesion considered to be of congenital origin. One patient was a seventeen year old boy who had been known to have aortic regurgitation since birth. He had the classic clinical features of severe aortic regurgitation with a blood pressure of 190/0 mm. Hg and suffered progressive cardiac decompensation. This patient died suddenly five months after operation and at autopsy the aortic valve was apparently normal, but the

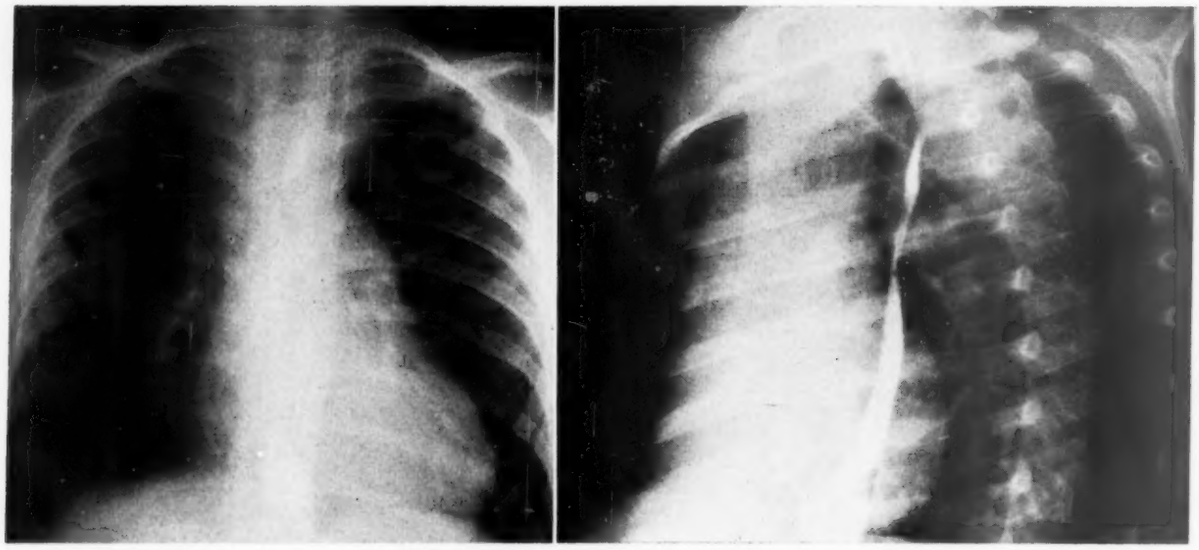

FIG. 8. Case III. Chest roentgenograms.

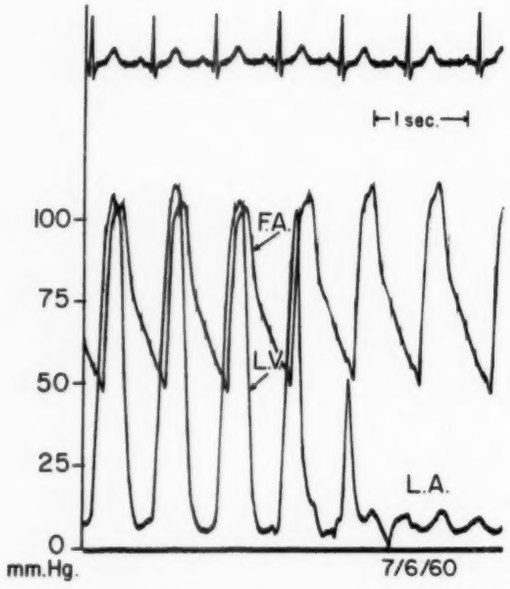

FIG. 9. Case III. Pressure pulses from the femoral artery (FA), the left ventricle (LV) and the left atrium (LA) obtained by means of transsepial left heart catheterization.

valve ring was "separated from its attachment to the aorta." Harvey's second patient was not described. Nadas [*16*] has observed three children with clinical evidence of aortic regurgitation, all of whom were symptom free after several years of observation. Systolic murmurs were audible in all, but no catheterization or angiocardiographic studies were performed in order to rule out an associated malformation.

The patients described in the present report had clinical and hemodynamic evidence of mild to moderate degrees of aortic regurgitation. All were asymptomatic males, and none had any of the clinical features suggestive of previous rheumatic fever, bacterial endocarditis or congenital syphilis. There was no change in the clinical picture in one patient observed over four years and in another over one year. Clinical examination of these patients revealed the pulse pressure to be slightly widened and, in addition to the characteristic diastolic murmur, a systolic murmur was audible at the base of the heart or along the left sternal border in all four patients. Two of them also had a prominent ejection sound. (Fig. 1.) The electrocardiograms either clearly showed the presence of left ventricular hypertrophy or suggested its presence in three patients. (Fig. 3), and was normal in the fourth patient. The chest roentgenograms revealed slight but definite dilatation of the thoracic aorta in all the patients and enlargement of the chambers of the left side of the heart in three. The pressures in the chambers of the right side of the heart and in the pulmonary artery were normal, and no associated circulatory shunts were detectable. Hemodynamically significant aortic stenosis was excluded in each instance by the demonstrated absence of a systolic pressure gradient between the left ventricle and the ascending aorta. There was no hemodynamic evidence of left ventricular failure; in no instance was the left ventricular end diastolic pressure elevated, and in the three

patients in whom it was measured the left atrial pressure was also normal. Retrograde thoracic aortography, performed in two patients, clearly revealed regurgitation of the contrast substance into the left ventricle; and in the other two patients, reversed flow in the aorta was demonstrated by means of an indicator-dilution technic.

The specific anatomic abnormality responsible for the aortic regurgitation in these patients is unknown. Massive dilation of the aorta was not noted in any of them and it would appear unlikely that Marfan's syndrome or Erdheim's cystic medionecrosis is present. Although fenestrations of the aortic valve cusps have been occasionally noted at autopsy in children, this abnormality rarely causes clinically detectable aortic regurgitation, and then only at older ages [*21,22*]. In one patient (Case II) the aortogram suggests that only two aortic cusps are present and it is possible that congenitally bicuspid aortic valves may be of etiologic importance in our patients.

In 1886, in a clinical-pathological description of bicuspid aortic valves, Sir William Osler recognized that this abnormality may lead to significant aortic regurgitation [*23*]. Since then a number of pathologists have presented gross and microscopic criteria for the differentiation of congenital and acquired bicuspid aortic valves [*24,25*], and have also indicated that the congential form may occur as an isolated entity or, more frequently, in association with other congential cardiovascular anomalies. It is well recognized that congenitally bicuspid aortic valves may produce no clinical abnormalities [*26*] or that they may result in various degrees of hemodynamically significant obstruction to left ventricular outflow [*27*]. When a bicuspid aortic valve produces combined stenosis and regurgitation, the stenosis is usually but not always the more significant lesion hemodynamically. It would seem possible, therefore, that in some instances this valvular deformity can result in regurgitation without hemodynamically detectable stenosis.

SUMMARY

The clinical, hemodynamic and angiographic features of four male patients with isolated congenital aortic regurgitation are described. In none was the regurgitation of major degree and in each instance left heart catheterization showed that there was no systolic gradient across the aortic valve. The presence of aortic regurgitation was substantiated by means of retrograde aortography or indicator-dilution curves. These patients appear to be the first in whom the diagnosis of isolated congential aortic regurgitation has been firmly established during life.

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The Graham Steell Murmur Versus Aortic Regurgitation in Rheumatic Heart Disease*

Results of Aortic Valvulography

VINCENT RUNCO, M.D., WILLIAM MOLNAR, M.D., CHARLES V. MECKSTROTH, M.D. *and* JOSEPH M. RYAN, M.D.

Columbus, Ohio

IT has become increasingly apparent that inaccurate preoperative diagnoses of valvular lesions in patients with rheumatic heart disease may seriously lessen the chances for good results following surgery. Many reports [*1–9*] concerning the results of mitral commissurotomy have commented upon the deleterious effects of coexisting mitral regurgitation and aortic valve lesions. The magnitude of these effects have become even more evident as long term results become available [*1*].

One of the problems in selecting candidates for mitral commissurotomy is the accurate evaluation of basal diastolic murmurs when mitral stenosis is associated with clinical evidence of pulmonary hypertension. This murmur has often been regarded as the Graham Steell murmur of relative pulmonic insufficiency. The clinical differentiation between the Graham Steell murmur and that of aortic regurgitation is extremely difficult if not impossible. Despite the need for a more proper interpretation of these basal diastolic murmurs, objective methods to better evaluate their origin have been scarce in the literature.

During the past five years, we have utilized retrograde aortic valvulography to more objectively differentiate relative pulmonic insufficiency from aortic regurgitation. The purpose of this communication is to report our findings with aortic valvulography in twenty-five patients with mitral stenosis and an associated basal diastolic murmur in whom the diagnosis of a Graham Steell murmur was entertained. Our results have shown that the great majority of these patients exhibited aortic regurgitation regardless of how strongly the clinical evidence favored relative pulmonic insufficiency.

METHOD AND MATERIAL

The detailed technic of aortic valvulography has been described previously [*9*]. A closed end catheter with side openings is introduced via the carotid or femoral artery into the ascending aorta with the tip of the catheter positioned at the level of the aortic sinuses. Depending on the estimated diameter of the aorta 30 to 40 cc. of concentrated iodine contrast material is injected under pressure over a period of two to three seconds. This delivers approximately 10 to 15 cc. of contrast medium per cardiac cycle for a total period of three or four cardiac contractions. This amount of contrast material is usually sufficient to demonstrate the aortic valve during four or five diastolic phases on serial roentgenograms taken at 4 to 6 frames per second on the Schonander biplane seriograph. The occurrence of each film exposure in relation to the electrocardiogram is recorded by an electronic oscillograph to help identify the proper phase of the cardiac cycle on each film.

To meet the criteria for valvular insufficiency, all films taken during consecutive diastolic phases must show regurgitation of the contrast material into the left ventricle. The severity of aortic insufficiency is graded from 1 to 4 plus depending on the amount of dye refluxed into the left ventricle: *One plus*—a small amount of contrast material is demonstrated in the outflow tract of the left ventricle on every film exposed during the different diastolic phases. However, the regurgitated contrast material disappears from the left ventricle during the intervening systolic periods. *Two plus*—a moderate amount of contrast material refluxes through the incompetent valve into

* From the Departments of Medicine, Radiology and Surgery, Ohio State University Hospital, Columbus, Ohio. This study was supported in part by the Central Ohio Heart Association. Presented in part at the 33rd Scientific Sessions of the American Heart Association, St. Louis, Missouri, October 1960.

TABLE I

PATIENTS WITH THE BASAL MURMUR CLINICALLY ATTRIBUTED TO A GRAHAM STEELL MURMUR

Patient, Age (yr.), Race and Sex	Clinical Diagnosis of Mitral Valve Lesion*	Systemic Blood Pressure (mm. Hg)	Intensity of Pulmonic Second Sound	Cardiac Fluoroscopy†		Electrocardiogram‡		Results of Left Atrial Puncture or Right Heart Catheterization§	Aortic Valvulography¶
				Left Ventricle	Aorta	Rhythm	Ventricular Enlargement		
B. S., 18, W, M	M.S.	100/80	Increased	Normal	Normal	N.S.R.	None	M.V.A. 0.8 cm.²	2 + A.I.
C. S., 16, W, F	M.S.	110/80	Increased	Normal	Small	N.S.R.	R.V.E.	M.V.A. 0.9 cm.² P.A. 55/23 (rest)	1 + A.I.
D. S., 23, W, F	M.S.	130/76	Increased	Normal	Normal	N.S.R.	Inc. RBBB; prob. R.V.E.	None	1 + A.I.
B. M., 25, W, F	M.S. ??M.I	110/68	Increased	Normal	Small	A.F.	R.A.D.	M.V.A. 1.4 cm.²	2 − 3 + A.I.
N. C., 39, N. F.	M.S. ??M.I	120/82	Increased	?? Enlarged	Normal	N.S.R.	R.A.D.; prob. R.V.E.	M.V.A. 0.7 cm.²	2 + A.I.
E. H., 42, W, F	M.S.	120/74	Increased	Normal	Normal	N.S.R.	Prob. R.V.E.	None	2 − 3 + A.I.
R. A., 30, W, F	M.S. M.I.	106/72	Increased	Probably enlarged	Normal	N.S.R.	R.V.E.	P.A. 88/35 (rest)	3 + A.I.
W. C., 33, W, F	M.S.	120/80	Increased	Normal	Normal	N.S.R.	Inc. RBBB	None	1 + A.I.
H. D., 46, W, F	M.S.	110/70	Increased	?? Enlarged	Normal	A.F.	R.V.E.	P.A. 90/40 (rest)	1 + A.I.
E. L., 41, W, F	M.S.	130/78	Increased	Normal	Normal	N.S.R.	R.V.E.	None	2 + A.I.
J. H., 42, W, F	M.S.	130/80	Increased	Normal	Normal	A.F.	Inc. RBBB	M.V.A. 1.4 cm.²	no A.I.
F. S., 43, W, F	M.S. ??M.I	120/80	Increased	Normal	Normal	N.S.R.	R.V.E.	None	no A.I.
J. B., 31, W, F	M.S.	120/82	Increased	Normal	Normal	A.F.	None	None	no A.I.

* M.S. = mitral stenosis. M.I. = mitral insufficiency.

† All had left atrial, right ventricular and main pulmonary artery enlargement by fluoroscopy.

‡ N.S.R. = normal sinus rhythm. A.F. = atrial fibrillation. Inc. RBBB = incomplete right bundle branch block. R.V.E. = right ventricular enlargement. R.A.D. = right axis deviation.

§ M.V.A. = mitral valve area. P.A. = pulmonary artery pressure mm. Hg.

¶ A.I. = aortic insufficiency.

the left ventricle during the diastolic phases with some contrast still remaining in the left ventricle during systole. *Three plus*—increasing amounts of regurgitated contrast material accumulate in the left ventricle on serial films. *Four plus*—marked regurgitation with the left ventricular chamber completely outlined by refluxed contrast material within the first cardiac cycle following injection.

Using these criteria for the roentgenographic demonstration of valvular incompetence, we have had no instances of false positive aortic regurgitation in over seventy patients with competent aortic valves subjected to basically the same procedure for coronary arteriography. The complications associated with this procedure have been minimal and are referred to elsewhere [*33*]. There were no complications in the patients included in this study.

This study includes twenty-five patients with rheumatic heart disease admitted to the University Hospital for evaluation as possible candidates for mitral valvulotomy. All the patients had mitral valve disease associated with a basal diastolic murmur and clinical evidence of pulmonary hypertension. The basal murmur was a soft, high-pitched, decrescendo diastolic murmur along the left sternal border that immediately followed the second heart sound and was heard best in the second and third left intercostal spaces. The patients were divided into two groups: Group 1 included thirteen patients with clinical evidence of severe mitral stenosis in whom the basal diastolic murmur following an accentuated pulmonic second sound was clinically thought to be a Graham Steell murmur of relative pulmonic insufficiency. (Table I.) In nine of these patients, the mitral valve lesion was considered to be pure mitral stenosis while the remaining four had evidence suggesting mitral regurgitation in addition to mitral stenosis. Group 2 was comprised of twelve patients with mitral valve disease in whom no definite conclusion as to the origin of the basal diastolic murmur could be made by the usual clinical methods. (Table II.) This was for the most part due to the frequent combined mitral stenosis and mitral regurgitation (eight patients) which makes the evaluation of basal diastolic murmurs even more difficult. Usually, when left ventricular enlargement is present with pure mitral stenosis, an associated basal diastolic murmur would most likely be due to aortic insufficiency. However, if mitral regurgitation is a complicating lesion it may of itself produce left ventricular enlargement and, therefore, the basal murmur need not represent aortic insufficiency.

TABLE II

PATIENTS WITH NO DEFINITE CONCLUSION REGARDING THE ORIGIN OF THE BASAL DIASTOLIC MURMUR

Patient, Age (yr.), Race and Sex	Clinical Diagnosis of Mitral Valve Lesion *	Systemic Blood Pressure (mm. Hg)	Intensity of Pulmonic Second Sound	Cardiac Fluoroscopy †		Electrocardiogram		Aortic Valvulography ¶
				Left Ventricle	Aorta	Rhythm ‡	Ventricular Enlargement §	
C. K., 35, W, F	M.S.	110/80	Increased	Normal	Small	A.F.	None	1+ A.I.
J. W., 36, W,M	M.S.; M.I.	122/78	Increased	Normal	Normal	A.F.	Inc. RBBB	1+ A.I.
A. C., 45, W,M	M.S.; M.I.	120/80	Increased	Probable enlargement	Small	A.F.	R.A.D.; inc. RBBB; probable R.V.E.	2+ A.I.
C. S. 44, W,M	M.S.	130/68	Increased	Normal	Normal	A.F.	None	2+ A.I.
M. M., 43, W,F	M.S.	110/62	Increased	Normal	Normal	N.S.R.	None	2+ A.I.
J. C. 22, W,F	M.S.; M.I.	130/70	Increased	Minimal enlargement	Normal	N.S.R.	None	1–2+ A.I.
D. C., 35 W,M	M.S.; M.I.	130/80	Increased	Probable enlargement	Normal	N.S.R.	Inc. RBBB	3+ A.I.
M. T., 40, W,F	M.S.; M.I.	100/60	Increased	Minimal enlargement	Normal	N.S.R.	Probable R.V.E.	2+ A.I.
D. R., 32, W,M	M.S.; M.I.	115/65	Increased	Moderate enlargement	Normal	A.F.	R.A.D.; inc. RBBB	no A.I.
H. C., 24, W,M	M.S.; M.I.	130/62	Increased	Moderate enlargement	Normal	A.F.	None	no A.I.
G. H., 48, W,F	M.S.	120/70	Increased	Probable enlargement	Probable enlargement	A.F.	None	no A.I.
I. S, 33, W,F	M.S.; M.I.	114/72	Increased	Probable enlargement	Normal	N.S.R.	None	no A.I.

* M.S. = mitral stenosis. M.I. = mitral insufficiency.

† All had left atrial, right ventricular and main pulmonary artery enlargement by fluoroscopy.

‡ N.S.R. = normal sinus rhythm. A.F. = atrial fibrillation.

§ Inc. RBBB = incomplete right bundle branch block. R.A.D. = right axis deviation. R.V.E. = right ventricular enlargement.

¶ A.I. = aortic insufficiency.

RESULTS

Ten patients in group 1 with the clinical diagnosis of a Graham Steell murmur were found to have aortic regurgitation by aortic valvulography. (Table I.) None of these patients had peripheral manifestations of aortic insufficiency, the lowest diastolic blood pressure being 68 mm. Hg and the widest pulse pressure 54 mm. Hg. All ten had evidence of pulmonary hypertension with an accentuated pulmonic second sound and definite left atrial, right ventricular and main pulmonary artery enlargement by fluoroscopy. The aorta was described as normal or small

in size. In three patients there was fluoroscopic evidence suggesting left ventricular enlargement as well. However, several investigators [*6,10–12*] have emphasized the difficulty in evaluating left ventricular chamber size in severe mitral stenosis with marked left atrial and right ventricular enlargement. Moreover, other studies in these three patients, including the electrocardiogram, pulmonary artery pressures and the determination of mitral valve area by left atrial catheterization, indicated severe mitral stenosis or pulmonary hypertension and supported the clinical diagnosis of relative pulmonic insufficiency. In addition, two of these three patients had evidence of mitral regurgitation which may have produced the possible left ventricular enlargement. Nine of the ten patients with demonstrable aortic regurgitation had either definite or suggestive evidence of right ventricular enlargement by the electrocardiogram. None of the patients had electrocardiographic evidence of left ventricular enlargement. One patient (B. S.) with a normal electrocardiogram was an eighteen year old white boy with severe mitral stenosis and definite fluoroscopic and auscultatory findings favoring the diagnosis of relative pulmonic insufficiency. The mitral valve areas determined in four patients by percutaneous left atrial catheterizations were between 0.7 and 1.4 cm.^{2} Right heart catheterizations were performed on three patients and the pulmonary artery pressures were between 55/30 and 90/40 mm. Hg at rest.

There were three patients in group 1 who did not demonstrate aortic regurgitation by valvulography. The clinical findings in these three patients were comparable in all respects to those that did exhibit aortic regurgitation, which illustrates the difficulty in clinically differentiating aortic from pulmonic insufficiency. In two of these patients the basal murmur disappeared following surgery while in one (F. S.) the murmur has remained unchanged two years after valvulotomy.

Of the twelve patients in group 2, eight demonstrated aortic regurgitation by valvulography. (Table II.) As in group 1, none of these patients exhibited peripheral signs of aortic insufficiency. All eight had an accentuated pulmonic second sound and roentgenologic evidence of left atrial, right ventricular and main pulmonary artery enlargement with a normal or small aorta. In addition, four of the eight patients had suggestive evidence of left ventricular enlargement by fluoroscopy. However, in all four, mitral regurgitation was a complicating factor and could have accounted for the left ventricular enlargement. None of the electrocardiograms demonstrated left ventricular enlargement but there was less evidence of right ventricular enlargement in this group than in group 1. Again, this may have been due to coexisting mitral regurgitation.

Four patients in group 2 did not show aortic regurgitation with valvulography. Even in retrospect we were unable to establish any auscultatory, fluoroscopic or electrocardiographic criteria to differentiate these four patients from the other eight in whom aortic regurgitation was demonstrated. This again emphasizes the difficulty in differentiating the basal diastolic murmurs by the usual clinical methods.

CASE REPORTS

CASE I. C. S., a seventeen year old white girl, was admitted to the Ohio State University Hospital for evaluation regarding mitral commissurotomy. The patient was known to have rheumatic heart disease and had symptoms of easy fatigability, dyspnea on exertion and cough. These symptoms had become progressively more severe. The physical examination revealed a blood pressure of 110/80 mm. Hg, a regular pulse at 88 per minute and a respiratory rate of 16 per minute. There was no apparent cardiomegaly. The mitral first sound was markedly accentuated. An opening snap was prominent and was followed by a loud low-pitched diastolic rumbling murmur with presystolic accentuation. There was no systolic murmur noted. The pulmonic second sound was markedly accentuated and split, and was followed immediately by a soft high-pitched diastolic murmur. This murmur was well localized to the pulmonic area and was not audible to the right of the sternum. The electrocardiogram demonstrated right ventricular enlargement. (Fig. 1.) The cardiac fluoroscopy demonstrated enlargement of the left atrium, right ventricle and main pulmonary artery. There was no left ventricular enlargement and the aorta was normal or small in size. (Fig. 2.) A simultaneous right and left heart catheterization was performed. The pulmonary artery pressure at rest was elevated to 55/23 mm. Hg and the mitral valve area was calculated at 0.9 cm.^{2} The clinical impression at this time was severe mitral stenosis with pulmonary hypertension and relative pulmonic insufficiency. However, a retrograde aortic valvulography was performed and demonstrated 1 plus aortic regurgitation. (Fig. 3.)

CASE II. E. L., a forty-one year old white woman, was admitted to University Hospital in 1958 with a

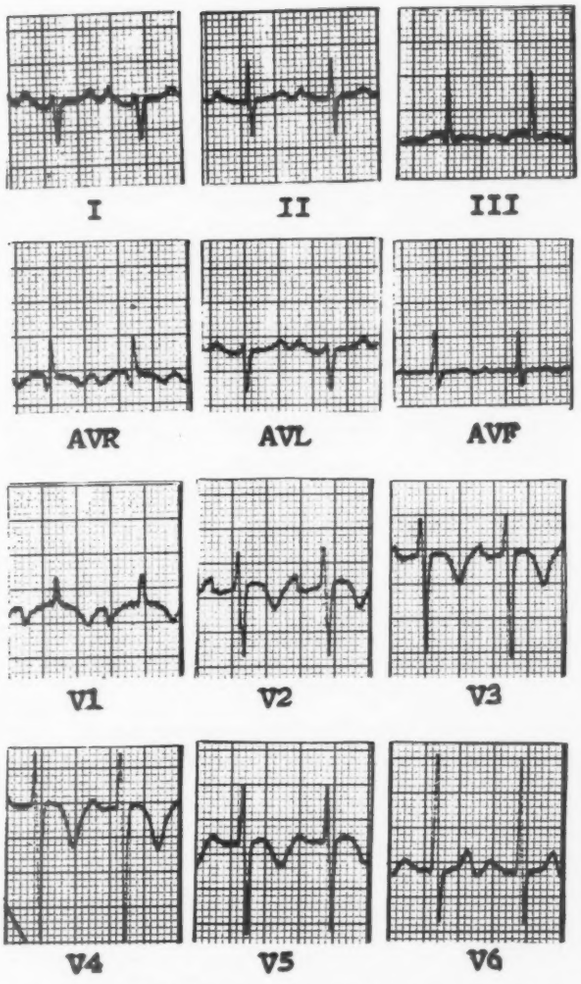

FIG. 1. Case 1. The electrocardiogram demonstrating right ventricular enlargement.

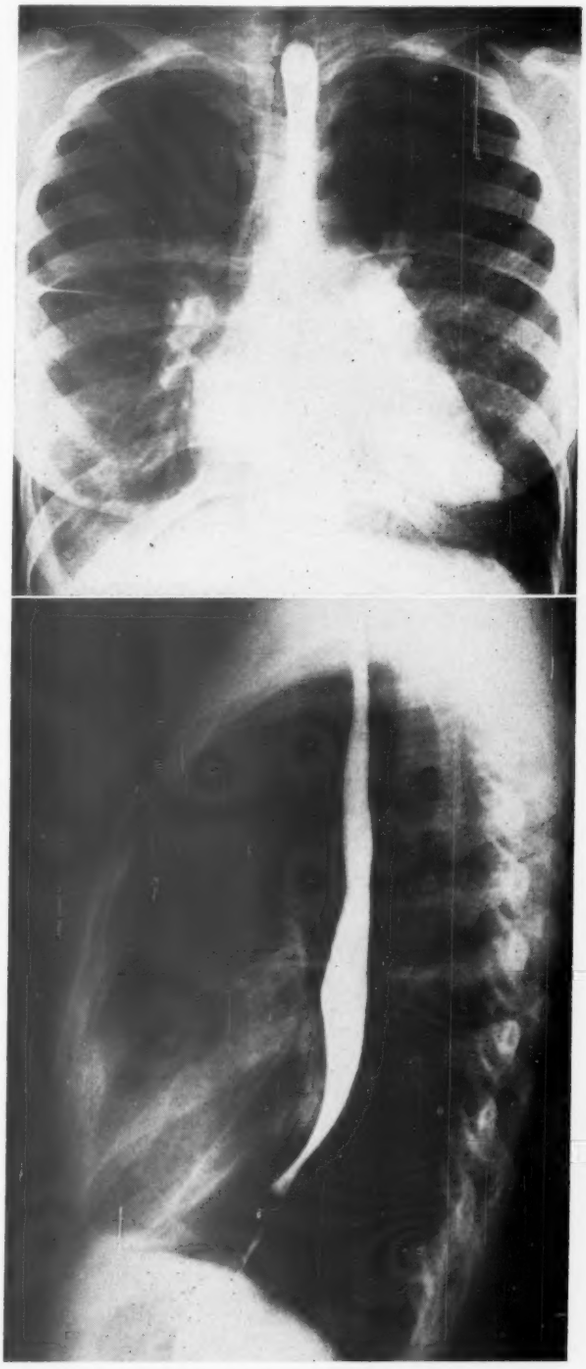

FIG. 2. Case 1. Posteroanterior and lateral views of the chest demonstrating enlargement of the left atrium, left atrial appendage and right ventricle. There is no apparent enlargement of the left ventricle as indicated by the clear posterior inferior retrocardiac space in the lateral view. The aorta is not enlarged.

history of acute rheumatic fever as a child, and symptoms of dyspnea on exertion, decreased exercise tolerance and easy fatigability during the ten years prior to admission. These symptoms progressively increased in spite of digitalization, salt restriction and the administration of diuretics. She was admitted for evaluation as a candidate for mitral commissurotomy. The physical examination revealed a blood pressure of 130/78 mm. Hg and a regular pulse of 78 per minute. The left border of cardiac dullness was just lateral to the midclavicular line in the fifth intercostal space. There was an accentuated mitral first sound, an opening snap and a long rumbling diastolic murmur at the apex with presystolic accentuation. The pulmonic second sound was markedly accentuated and was followed by a soft high-pitched diastolic murmur heard best at the second and third left intercostal spaces. The electrocardiogram demonstrated right ventricular enlargement. (Fig. 4.) Cardiac fluoroscopy showed left atrial and right ventricular enlargement with enlarged main pulmonary arteries. The aorta and left ventricle were not enlarged. (Fig. 5.) The clinical impression was mitral stenosis with pulmonary hypertension and a Graham

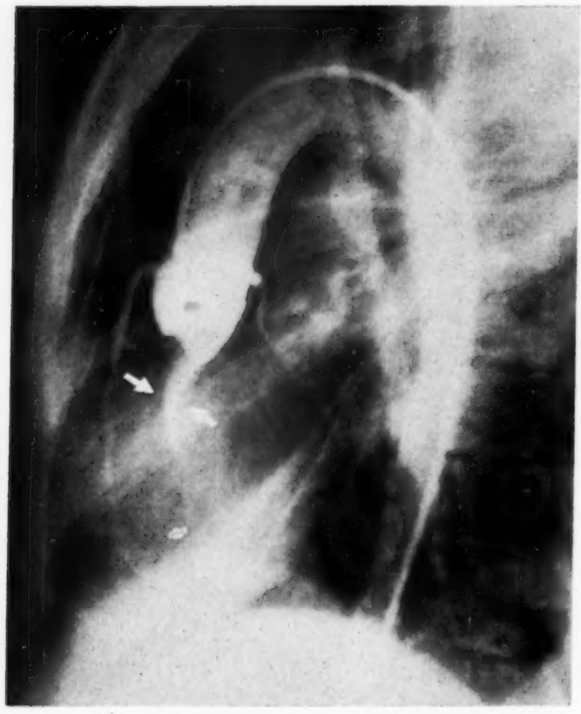

FIG. 3. Case I. Aortic valvulography demonstrating the refluxed contrast material just below the aortic valve leaflets (arrows). This regurgitation was demonstrated on all of the films taken during the diastolic phases of the cardiac cycles and represents 1 plus aortic regurgitation.

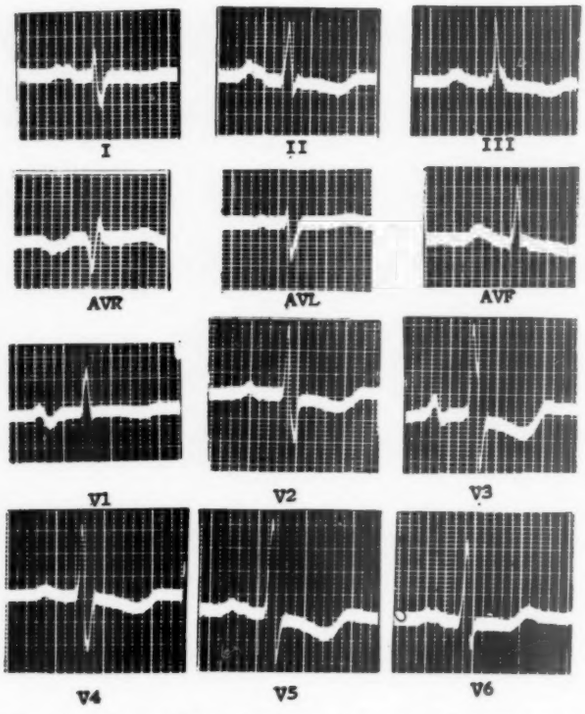

FIG. 4. Case II. The electrocardiogram demonstrating notched P waves and right ventricular enlargement.

FIG. 5. Case II. Posteroanterior and lateral views of the chest demonstrating left atrial, right ventricular and main pulmonary artery enlargement. There is no good evidence of left ventricular enlargement and the aorta was normal in size.

Steell murmur. Aortic valvulography was performed and 2 plus aortic regurgitation was demonstrated. (Fig. 6.)

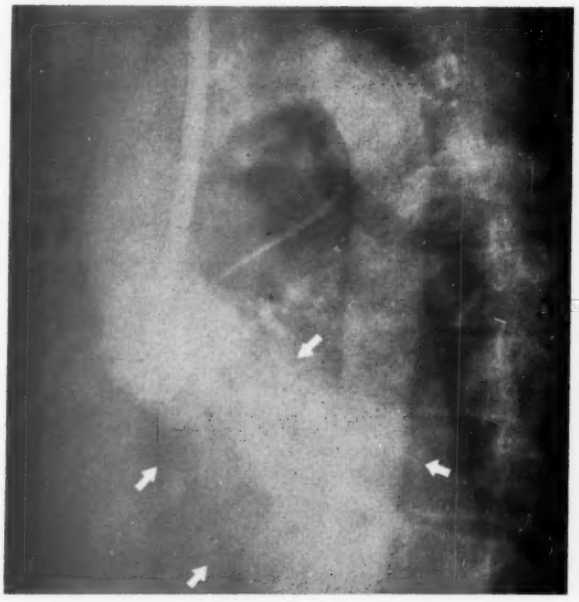

FIG. 6. Case II. Aortic valvulography demonstrating considerable refluxed contrast material in the left ventricle during diastole (arrows). This regurgitation was present on all of the films taken during diastole and there was demonstrable residual contrast material during the intervening systolic periods. This represents 2 plus aortic regurgitation.

COMMENTS

The surgical approach to acquired heart disease has made an accurate preoperative diagnosis of the valvular lesions essential if long term benefit is to be achieved and if the postoperative results are to be more accurately evaluated. Yet, numerous reports [*1,2,4,6,13*] have appeared in the literature emphasizing the frequent disparity between the clinical appraisal of the valvular lesions and the actual findings at the time of surgery. Frequently these errors in clinical evaluation have resulted in either no improvement or a worsening of the patient's course following surgery [*1,5–9*]. Some of the shortcomings of clinical diagnosis have been circumvented by utilizing more objective means of evaluation, including right and left heart catheterizations, indicator dilution studies and cardioangiography. These technics have considerably improved the selection of patients for mitral commissurotomy and the subsequent surgical results. However, the significance of basal diastolic murmurs in mitral valve disease has not been adequately studied by objective means in the past and continues to present a problem in differential diagnosis.

Clinically the Graham Steell murmur of relative pulmonic insufficiency has frequently been invoked to account for this basal murmur in mitral stenosis if there is no left ventricular enlargement or peripheral manifestations of aortic regurgitation [*1,2,10,14–17*]. Other criteria to establish this diagnosis include roentgenographic or electrocardiographic evidence of right ventricular enlargement [*2,10,16,19,20*], enlarged, pulsating main pulmonary arteries [*2,16,19,20*], a small aorta with no evidence of aortic stenosis [*2,16,19,20*], and localization of the murmur to the second and third left intercostal spaces [*16,18,20*]. Using these clinical criteria, the reported incidence of relative pulmonic insufficiency in rheumatic heart disease is frequent, and it has been estimated in some series [*17*] that 10 to 15 per cent of patients with mitral stenosis have a Graham Steell murmur. However, the majority of clinical experiences have been accompanied by little or no supporting evidence to substantiate the diagnosis, and the true incidence still remains unknown.

As shown by our results, the clinical differentiation between relative pulmonic insufficiency and aortic regurgitation is often impossible regardless of the clinical criteria used. Others [*6, 15,21–23*] have had similar experiences. The character, intensity and location of the murmurs may be identical, and all of the usual methods of clinical evaluation may be misleading. The pulmonic second sound need not correlate with the degree of pulmonary hypertension [*23*]. Electrocardiographic evidence of right ventricular enlargement may not be present in spite of severe mitral stenosis and high pulmonary artery pressures [*2,12,24,25*]. Left ventricular enlargement is extremely difficult to evaluate fluoroscopically or electrocardiographically in the presence of marked left atrial and right ventricular enlargement [*6,10–12*]. Its significance is even more difficult to evaluate in the presence of coexisting mitral regurgitation. The usual hemodynamic effects of aortic regurgitation as a result of increased left ventricular stroke volume and an accelerated diastolic run off are well known. However, when combined with mitral stenosis the usual clinical evidence of aortic regurgitation may not be present due to the obstruction to left ventricular inflow with a resultant decreased left ventricular stroke vol-

ume [*6,7,13*]. As seen in our patients, none exhibited the peripheral manifestations of aortic insufficiency. These and other factors were frequently overlooked in previous reports concerning the Graham Steell murmur.

We believe that aortic valvulography has offered an objective means to evaluate better the basal diastolic murmur in patients with mitral stenosis. Our results would indicate that the great majority of these patients have aortic regurgitation regardless of the clinical evidence suggesting relative pulmonic insufficiency. Collins, Braunwald and Morrow [*22*] have obtained similar results using indicator dilution technics. They found evidence of aortic regurgitation in six of seven patients suspected clinically of having pulmonic insufficiency.

The detection of this frequently unsuspected aortic regurgitation preoperatively has important surgical implications. It is generally accepted that patients with mitral stenosis and a basal diastolic murmur due to pulmonary hypertension should do well with commissurotomy [*1,2,9,10,26*]. However, in some patients who appear clinically to be ideal candidates for mitral commissurotomy, the anticipated good results following surgery are not forthcoming. The presence of unsuspected aortic regurgitation may in part account for some of the disappointing results. Others [*5,6,9,17,27–29*] have previously referred to the deleterious effects of coexisting aortic regurgitation following mitral valvulotomy. We have had similar experiences. We realize that many factors may unfavorably influence the results of mitral commissurotomy but we have been impressed with the poor results following surgery in patients with associated aortic regurgitation of 2 plus or more as demonstrated by valvulography. Experimental work [*28*] has further suggested that the adverse consequences of aortic regurgitation following mitral commissurotomy may be especially profound if mitral insufficiency is inadvertently produced or increased at the time of surgery. To evaluate better the significance of aortic regurgitation and to improve further the selection of patients for mitral commissurotomy we believe that aortic valvulography should be performed preoperatively in all patients who have a basal diastolic murmur. If significant aortic regurgitation (greater than 2 plus) is demonstrated, it is doubtful that valvulotomy will be of benefit and may actually worsen the patient's course by increasing the severity of the aortic regurgitation when obstruction of the mitral valve is relieved. We have not yet determined what degree of aortic regurgitation will still permit a beneficial result with mitral valvulotomy. Recently commissurotomy has been performed in three patients in this study with 1 plus regurgitation, but the follow-up has not been sufficiently long to permit any conclusions.

To date, we have not found a practical and reliable method to detect pulmonic valve incompetence, especially with minor degrees of regurgitation. Therefore, in this series we cannot definitely exclude the presence of coexisting functional pulmonic insufficiency in the patients found to have aortic regurgitation. Some investigators [*22,31*] have attempted to evaluate pulmonic regurgitation by the injection of indicator solutions in the pulmonary artery via right heart catheterization and sampling proximal to the valve in the right ventricle. However, the results by this method may be subject to considerable error. Previous studies [*31,32*] have commented on the problems of determining regurgitant flow by indicator dilution technics. False positive and false negative results may occur from incomplete mixing of the indicator, faulty positioning of the injection site and distortion of valve leaflets by the catheter. The location of the sampling site may also produce appreciable error in the method. Dickens, Rober and Goldberg [*21*] attempted to evaluate functional pulmonic regurgitation in mitral stenosis by comparing the pulmonary artery pressure tracings of those patients considered to have a Graham Steell murmur with the pressure tracing of a proved case of congenital pulmonic insufficiency. None of the patients considered to have functional pulmonic insufficiency demonstrated the typical pressure contour and low pulmonary diastolic pressure seen in the congenital case. From their results, they questioned the existence of functional pulmonic insufficiency in the presence of normal valves. Although conclusive objective proof is lacking, it would appear to us that relative pulmonic insufficiency does exist in some cases of severe pulmonary hypertension, especially in congenital heart lesions. However, we believe its incidence in rheumatic heart disease has been greatly overestimated.

In conclusion, it would appear that the true incidence of relative pulmonic insufficiency in rheumatic heart disease is unsettled. Its actual

existence has even been questioned by some. Although this investigation does not solve the problem of pulmonic insufficiency, our results do indicate that unsuspected aortic regurgitation is present in the great majority of patients thought to have a Graham Steell murmur. The detection of this aortic regurgitation preoperatively is important not only in the selection of patients for mitral commissurotomy but also in determining the relative importance of associated aortic regurgitation on the postoperative results. We believe that aortic valvulography has offered a safe, objective and accurate means to detect and grossly quantitate aortic regurgitation and should be used in the preoperative evaluation of basal diastolic murmurs in patients being considered for mitral commissurotomy.

SUMMARY

To differentiate more objectively aortic regurgitation from relative pulmonic insufficiency in rheumatic heart disease, aortic valvulography was performed in twenty-five patients with mitral stenosis in whom the diagnosis of a Graham Steell murmur was entertained. The majority of patients (eighteen) were shown to have aortic regurgitation in spite of clinical findings favoring relative pulmonic insufficiency. The results of this study would indicate that the incidence of a Graham Steell murmur in rheumatic heart disease has been greatly overestimated. The surgical implications in the detection of this frequently unsuspected aortic regurgitation prior to mitral commissurotomy are discussed.

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Hypoaldosteronism as a Cause of Hyperkalemia and Syncopal Attacks in a Patient with Complete Heart Block*

COSTAS T. LAMBREW, M.D., SUSAN T. CARVER, M.D., RALPH E. PETERSON, M.D. *and* MELVIN HORWITH, M.D.

New York, New York

HYPOALDOSTERONISM is a rare and only recently recognized isolated secretory insufficiency of the adrenal cortex. This entity was first described by Hudson et al. [*1*] in a patient with complete heart block. A second patient in whom this secretory defect was documented was described by Hill and his associates [*2*]. It is the purpose of this paper to report a third case of isolated hypoaldosteronism and to substantiate further its relationship to ventricular asystole in a patient with complete heart block.

CASE REPORT

C. B. (NYH 772579), an eighty year old retired Italian-born marble cutter, was admitted to The New York Hospital with a complaint of shortness of breath. He dated the onset of his illness to two years prior to admission, when exertional dyspnea and minimal edema of the ankles first developed. He had noted infrequent palpitations and, on rare occasions, dizziness. He gave no history of chest pain, hypertension, cardiac murmurs, renal disease or syncope.

Physical examination revealed a well developed, jaunty, elderly white man who appeared neither acutely nor chronically ill. The blood pressure was 210/50 mm. Hg in the supine position; the apical pulse was felt at a rate of 32 per minute and was regular. Moderate retinal arteriolar narrowing was observed. The neck veins were full, but did not distend further on hepatic pressure. A few fine rales were heard at the base of the left lung posteriorly. The apical first sound was variable in intensity. A soft systolic murmur was audible over the entire precordium. The liver was not enlarged. There was 1 plus pitting edema of the ankles.

The urinalysis and hemogram obtained on admission were within the limits of normal. The reaction to the Mazzini test was negative. Results of liver function tests and the serum transaminase, calcium, phosphorus and carbon dioxide combining power were normal. The serum sodium was 140 mEq./L., chlorides 107 mEq./L. and potassium 4.3 mEq./L. The blood urea nitrogen was 17 mg. per cent and the fasting blood sugar 114 mg. per cent. Maximal clearance of urea was 54 per cent of normal in the first hour, and 39 per cent in the second hour with good flow of urine. A diabetic glucose tolerance curve was observed. The chest roentgenogram showed moderate cardiac enlargement with left ventricular preponderance and pulmonary congestion. The electrocardiogram obtained on admission showed complete heart block, with a ventricular rate of 30 per minute, and non-specific abnormalities of the T waves and R-T segments. The venous pressure at the estimated level of the right atrium was 125 mm. of saline solution. The intravenous pyelogram was within normal limits.

Since the patient was in mild congestive heart failure he was given a 3 gm. salt diet and meralluride was administered. A satisfactory diuresis ensued. On the second hospital day an infusion containing 100 mg. of cortisol was administered to determine its possible effect on the heart block [*3*]. There was no change in cardiac rhythm or in serum potassium levels. Beginning on the fifth hospital day the patient was given 1.2 mg. of digitoxin over a forty-eight–hour period. On the eighth day he convulsed and was found to be pulseless. A subcutaneous injection of 0.2 mg. of isoproterenol was followed by resumption of an idioventricular rhythm. The serum potassium was found to be 6 mEq./L. and fell to 4.9 mEq./L. following the intravenous injection of dextrose in water, with insulin. The blood urea nitrogen drawn on the following morning was 58 mg. per cent. The administration of digitoxin was discontinued at this time because of the possibility that its depressant effect may have contributed to the onset of the asystolic episodes.

During subsequent observation, there were frequent episodes of extreme bradycardia and ventricular

* From The Department of Medicine and The Metabolic Unit of The Russell Sage Institute of Pathology, The New York Hospital–Cornell Medical Center, New York, New York.

asystole. These were preceded by apprehension and restlessness, and closely followed by generalized seizures. Single subcutaneous or intravenous injections of isoproterenol were temporarily efficacious in restoring his usual cardiac rhythm and rate. Subsequently, an adequate ventricular rate could be maintained only by continuous intravenous infusion of isoproterenol; the resultant rhythm was characterized by multifocal ventricular complexes. At this time the serum potassium was 6.1 mEq./L. The patient then became refractory to isoproterenol, and ventricular systoles could be stimulated only by use of the electrical pacemaker for a period of eighteen hours, during which the serum potassium rose to 7 mEq./L. The administration of two intravenous infusions of 500 ml. dextrose in water, with insulin (25 units), was followed by a fall in serum potassium to 5.8 mEq./L. in twelve hours. Pacemaker stimulation was then discontinued without event.

During the next two months there were two more episodes of prolonged ventricular asystole requiring continuous use of the pacemaker; both episodes were *preceded* by elevation of the serum potassium to levels of 6 mEq./L. or greater. Both episodes were terminated successfully with the use of pacemaker stimulation and infusion of dextrose in water, with insulin. With a third episode, melena developed, and the hematocrit fell to 24 per cent. The patient was given a transfusion and bleeding subsided, not to recur. Roentgenographic examination of the upper gastrointestinal tract at a later date failed to reveal a lesion.

The electrocardiogram was monitored constantly for nearly a month. Whenever departure from the usual ventricular focus or progressive decrease in the ventricular rate was observed, serum potassium was invariably found to be elevated in the range of 5.5 to 6 mEq./L. Hence infusions of dextrose in water, with insulin, were administered prophylactically at these times in an effort to abort the occurrence of ventricular asystole. Dietary potassium was restricted to 3 gm./day and salt intake was liberalized to 5 gm./day. Ambulation was begun without event. Over the next seven weeks only two brief episodes of asystole occurred, associated with serum potassium levels of 6 and 6.7 mEq./L., respectively. Frequent electrolyte determinations showed the serum sodium concentration to vary between 129 and 137 mEq./L., the blood urea nitrogen between 21 and 28 mg. per cent. The latter became elevated to values between 54 and 78 mg. per cent *following* periods of asystole. It was noted that the alterations in serum potassium and sodium always preceded the episodes of asystole and the subsequent elevation of the blood urea nitrogen.

After further metabolic studies (Results of Metabolic Studies) the patient was discharged to his home on a 3 gm. salt diet without restriction of dietary potassium, and given 0.05 mg. of 9-alpha-fluorohydrocortisone every other day. On this regimen the patient felt quite well and was free of edema; the heart rate remained stable at about 40 per minute. The electrocardiogram showed persistence of complete heart block. The serum potassium was never found to exceed 5.4 mEq./L. One month after discharge the patient was readmitted because of dyspnea, orthopnea and dependent edema which had developed over a three-day period. He denied any recurrence of syncope. Upon examination, the findings were essentially unchanged save for the presence of 4 plus edema of the ankles, distended neck veins and bilateral basilar rales. The patient was not in acute distress at the time of admission; however, thirty minutes thereafter he convulsed and the electrocardiogram showed asystole. There was no response to pacemaker stimulation or to isoproterenol. The patient was pronounced dead forty minutes after admission. Unfortunately, permission for postmortem examination could not be obtained. Laboratory data obtained immediately upon admission were as follows: hematocrit 36 per cent, serum sodium 139 mEq./L. and serum potassium 4.8 mEq./L.

RESULTS OF METABOLIC STUDIES

Electrolyte Response to 9-alpha-Fluorohydrocortisone and Sodium Restriction. These investigations were carried out over a twenty-five day period. For the first eight days the patient was given 0.1 mg./day of 9-alpha-fluorohydrocortisone orally. Unfortunately, because of initial lack of understanding and cooperation on the part of the patient, urine collections were incomplete and determinations of urinary electrolyte excretion therefore not valid. Sodium and potassium intakes during this time were both 60 mEq./day. Serum sodium rose from 131 to 143 mEq./L., and serum potassium fell from 5.5 to 3.7 mEq./L. after three days of therapy with 9-alpha-fluorohydrocortisone.

After steroid therapy was discontinued, an indwelling Foley catheter was inserted to insure completeness of urine collections. Over the next five days, the mean sodium intake was 45 mEq. and the mean potassium intake 53 mEq./day. The mean sodium excretion was 65 mEq. and mean urinary potassium 36 mEq./day.

Following completion of this collection period, sodium intake was markedly restricted to 1.5 mEq./day, and dietary potassium was maintained at 38 mEq./day. On this program the mean level of urinary sodium content fell only moderately to 47 mEq./day, and the mean urinary potassium fell to 30 mEq./day. On the ninth and tenth days of sodium restriction, 40 units of adrenal corticotropin in 500 ml. of

TABLE I
PLASMA CORTISOL AND CORTICOSTERONE

	Patient C. B. (μg. %)	Normal Levels [7,8] (μg. %)
Cortisol*		
Control	14	6–25
Post ACTH	33	30–60
Corticosterone†		
Control	2	0.4–2
Post ACTH	9	5–10

* Determined according to the modified method of Silber and Porter [4].

† Determined according to the method of Peterson [5].

dextrose in water were infused over an eight-hour period. Twenty-four hour urinary sodium excretion fell markedly to 6.9 mEq. after the first day, and fell further to 2.1 mEq. after the second day of stimulation. There was no significant change in the serum electrolyte concentration during this collection period: the value for serum sodium was 141 to 147 mEq./L. and for potassium 4.5 to 5.1 mEq./L. Blood urea nitrogen varied between 8 and 18 mg. per cent.

Adrenocortical Function. Adrenal corticotropin infusion reduced circulating eosinophils from 78 to 0. The control urinary excretion of 17-hydroxycorticoids was 2.5 and 3.9 mg./day, and the excretion of 17-ketosteroids was 4.3 and 5.4 mg./day. After two days of adrenal corticotropin the excretion of 17-hydroxycorticoids rose to 12 mg., and that of 17-ketosteroids to 16 mg./day.

The steroid content of pooled plasma was also determined. Control plasma cortisol was 14 μg. per cent, rising to 33 μg. per cent after stimulation. Control plasma corticosterone was 2 μg. per cent, rising to 9 μg. per cent after stimulation. (Table I.)

Aldosterone Values. Urinary and plasma aldosterone levels were determined by the double isotope derivative dilution method of Kliman and Peterson [6]. Urinary levels during the control period were 2 and 8 μg./day on two successive days. There was no significant change with marked salt deprivation. On the two days of stimulation, the levels were 3 and 4 μg./day, respectively. The plasma aldosterone level following salt restriction and adrenal corticotropin stimulation was 0.05 μg. per cent. (Table II.)

TABLE II
URINARY AND PLASMA ALDOSTERONE LEVELS

Regimen	Urine (μg./day)		Plasma (μg./day)	
	Patient	Normal [9]	Patient	Normal [9]
Control diet	2,8	5–20	...	0.04–0.08
1.54 mEq. sodium diet	3,8	15–60	...	...
1.54 mEq. sodium diet plus ACTH	3,4	15–60	0.05	0.08–0.16

COMMENTS

The diagnosis of a selective deficiency of aldosterone secretion by the adrenal cortex must depend upon the demonstration of a marked decrease of urinary aldosterone excretion in the presence of normal glucocorticoid function.

The patient showed none of the clinical manifestations of Addison's disease. The response of total circulating eosinophils to adrenal corticotropin stimulation was normal. Control levels of urinary steroids were low normal, and their response to adrenal corticotropin stimulation was adequate. Control levels of plasma cortisol and corticosterone were normal, as was their response to stimulation [7,8].

There was probably some degree of impaired renal function in this patient, as reflected in the moderately decreased clearance of urea. However, the highest random urinary specific gravity was 1.020, and intravenous pyelography failed to reveal any abnormality. The concentration of serum sodium rose, and that of serum potassium fell to normal when 9-alpha-fluorohydrocortisone was administered. Furthermore, urinary sodium excretion fell to extremely low levels during adrenal corticotropin infusion. Hence it was believed that the alterations in serum electrolytes and the inefficient conservation of sodium during the period of sodium deprivation must be ascribed to an inadequacy of aldosterone secretion, and not to a disordered intrinsic responsiveness of the renal tubular sodium conserving mechanism.

Control levels of urinary aldosterone were low, and there was no rise with salt restriction. The plasma aldosterone level, determined following the period of sodium restriction and adrenal corticotropin stimulation, was within the range of normal for a patient with *normal* sodium intake [9].

During the course of the metabolic study period, dietary potassium was maintained at a

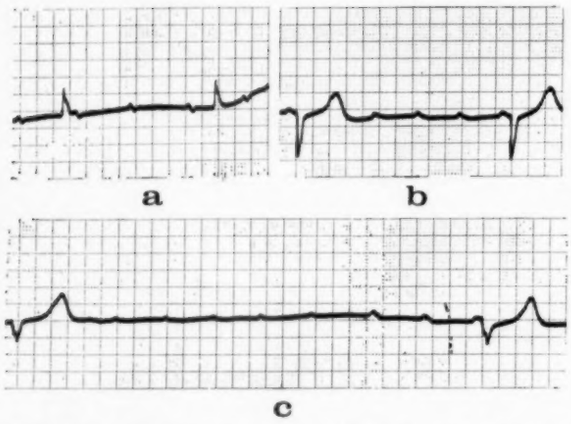

FIG. 1. Patient C. B. Three strips in lead II of the electrocardiogram are reproduced, demonstrating complete heart block with varying rate and site of origin of the idioventricular pacemaker. The ventricular rate decreases as the serum K^+ rises: *a*, serum K^+, 4.1 mEq./L.; ventricular rate, 32 per minute. *b*, serum K^+, 6.1 mEq./L.; ventricular rate, 23 per minute. *c*, serum K^+, 7.0 mEq./L.; ventricular rate, 11 per minute.

low level (38 mEq./day). Laragh [*10*], in a study of normal subjects, found that a normal or increased potassium intake was necessary to demonstrate the expected increase in urinary aldosterone with a low salt stimulus. However, Johnson [*11*] subsequently demonstrated that although low potassium intake did decrease aldosterone output somewhat, there was still a two- to sixfold rise in the urinary aldosterone level with sodium restriction despite the concomitant restriction of dietary potassium. The rise in urinary aldosterone did seem to occur more slowly under these circumstances. It was therefore concluded that the effect of sodium restriction on aldosterone output seemed to predominate over the modifying effect of low potassium intake. It may then be assumed that the patient described herein was subjected to an adequate stimulus, and that the low level of aldosterone excretion represents a true secretory deficiency of this hormone.

The relationship of hyperkalemia to deterioration of cardiac rhythm and syncopal attacks in this patient is incontrovertible. As in the case described by Hudson [*1*], these attacks were precipitated in the early days of hospitalization when salt was restricted. An elevation of serum potassium above 5.5 mEq./L. could invariably be predicted when the monitoring electrocardiogram revealed a departure (multiple ventricular foci, slowing of rate) from the usual electrocardiographic pattern, or when asystole occurred. (Fig. 1.) The effect of an elevated serum potassium in slowing the ventricular rate in this patient may be ascribed to a depression of pacemaker activity, and to a retardation of impulse propagation [*12*]. Hence the patient's already disordered myocardial conduction system became a sensitive indicator of the serum potassium level.

Skanse and Hokfelt [*13*] described a patient with no detectable urinary aldosterone during normal and restricted sodium ingestion. However, urine and serum electrolyte changes were normal and did not follow the pattern seen in the patients studied by Hudson [*1*], Hill [*2*] and in the present case. There were no abnormalities of atrioventricular conduction. The patient's symptoms were not alleviated by adequate mineralocorticoid therapy.

The association of hypoaldosteronism with complete heart block in this patient, and in the patient described by Hudson, is indeed quite unusual. In both cases neither hyperkalemia nor recurrence of syncopal attacks was observed following treatment with 9-alpha-fluorohydrocortisone. The terminal episode in our patient was not typical of his previous attacks, although it certainly seemed to be a cardiac death. However striking the coincidence in these two cases may be, it is important, at the present time, not to associate complete heart block and hypoaldosteronism as a syndrome. The clinical picture in both of these patients is due to the effects of hyperkalemia secondary to hypoaldosteronism on a pre-existing complete atrioventricular block.

SUMMARY

A patient with complete heart block in whom recurrent ventricular asystole was precipitated by hyperkalemia is described. The elevation in serum potassium is believed to have been due to isolated hypoaldosteronism, in view of the presence of low plasma and urinary aldosterone levels during sodium restriction, and the absence of significant impairment of glucocorticoid function. The electrolyte alterations, other than hyperkalemia, consisted of hyponatremia and inefficient renal conservation of dietary sodium. The serum electrolyte abnormalities were corrected and the syncopal attacks abolished upon administration of 9-alpha-fluorohydrocortisone. It is noted that no "characteristic" clinical syndrome can yet be associated with hypoaldosteronism, save that resulting from second-

ary hyperkalemia in the two patients with atrioventricular block thus far described.

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Reviews

Colonic Motility*

A Critical Review of Methods and Results

NAZIR A. CHAUDHARY, M.B., D.PHIL. *and* SIDNEY C. TRUELOVE, M.D.
Oxford, England

THE movements of the human colon have received comparatively little careful study. Most of our knowledge of colonic motility comes from work on animals, and much of this was conducted under highly artificial conditions and made use of recording methods which are far from ideal in the light of modern knowledge. The few studies which have been made in man have seldom used the best available methods of recording and for the most part have been small in scope.

REVIEW OF METHODS

The following methods have been used for the study of motility of the gastrointestinal tract:

Direct Observation. Direct observation of the external surface of the gut: In animals, by floating the viscus in warm saline solution after the animal had been anaesthetised with ether and the spinal cord had been destroyed below the fifth or sixth thoracic segments. The stimulus to movement was distention produced by the forcible passage of gruel [*1*]. In human beings in whom segments of the gut had prolapsed as a result of surgical operation or as a result of trauma [*2,3*].

Direct observation of the mucosal surface of the gut: In animals, segments of the gut were exposed, isolated and brought on to the abdominal wall; these segments were then opened longitudinally and the mucosal edges were sutured to skin margins after an equivalent area of skin had been removed [*4*]. In human beings, by observation of mucosa of prolapsed segments of the bowel or by observation through a sigmoidoscope in intact subjects [*5,6*].

Roentgenologic Methods. Studies have been made after ingestion of radiopaque substances employing the following methods: (1) visual observation under a fluoroscopic screen; (2) cineradiography; and (3) transit times, i.e., the determination of the time taken for the passage of radiopaque material from one part of the digestive tract to another.

Balloon Technics. Water-filled or air-filled balloons have been introduced into the lumen of gut and, after being connected to a recording device, have been extensively used for the study of gastrointestinal motility. Probably the first workers to use the balloon technic were Legros and Onimus [*7*] in 1869, and balloons were first used to record motility in man in 1887 by Pfunger [*8*] who introduced them through a fistula in the stomach.

Intraluminal Pressure Recording Technics. Changes in intraluminal pressure in the gastrointestinal tract have been recorded and interpreted in terms of motility [*9,10*] employing the following methods: (1) Water-filled or air-filled tubes with open ends lying inside the gut, the other ends being connected to suitable manometers. (2) An electromagnetic transducer which was introduced into the lumen of the gut. The transducer had a self-supporting centre-tipped coil which formed two arms of a balanced induction bridge. Changes in intraluminal pressure caused proportional displacement of an elastically mounted iron core, the resulting change being conveyed by a wire to a recording device so that electrical imbalance was recorded in terms of pressure [*11*]. (3) A rigid plastic capsule (radio telemetering capsule) 3 cm. in length, 1 cm. in diameter and 5 to 6 gm. in weight was swallowed by the patient. The capsule contained a frequency modulation transistor radio transmitter, power being supplied by a tiny replaceable battery. Pressure on the sensitive end changed the inductance of the internal circuit. This change modulated the frequency of the oscillations generated by the transmitter. A frequency modulation receiver placed near the patient demodulated the signals, and pressure fluctuations were displayed oscilloscopically and recorded permanently on paper [*12*].

CRITICAL EVALUATION OF VARIOUS METHODS

Direct Observation. This is a useful method of study but it does not allow us to make any quantitative observations. A permanent record of motility is not available for future reference, and observations, no matter how carefully noted, depend only on the impression of the observer.

Roentgenologic Methods. These are also useful

* From the Nuffield Department of Clinical Medicine, University of Oxford, Oxford, England.

methods but suffer from a number of serious drawbacks. (1) *Visual* observation under a fluoroscopic screen after the administration of radiopaque material has some of the same disadvantages as direct observation, e.g., the interpretation of findings depends on the subjective opinion of the observer. A more serious disadvantage is that with conventional x-ray apparatus the period of observation must be brief because of risk to the subject. The safe period of observation can be greatly lengthened by the use of an image intensifier, although at present most image intensifiers cover a diameter of 5 inches so that the zone of observation is restricted. (2) *Cineradiography* has marked advantages over visual observation on a fluoroscopic screen or with an image intensifier. The salient advantage is that a permanent record is made of the observations so that they can be studied and analysed at leisure. Cineradiography is practicable in human subjects only for short periods with conventional apparatus. The use of an image intensifier allows observation for longer periods. Nevertheless, the total period of continuous observation must be in terms of minutes. For many purposes we may wish to study the activity of the gastrointestinal tract for hours. (3) *Transit times* give a rough measure of propulsive activity but are useless for a detailed study of the movements of any particular part of the gastrointestinal tract.

The Balloon Technic. Water-filled or air-filled balloons connected to water manometers or optical manometers have been widely used for recording motility in the past and are still used by a large number of workers. The main advantage of this technic lies in the economy and easy availability of the components of the system. Notwithstanding these advantages, their use for studying gastrointestinal motility has serious drawbacks. These have been fully discussed by Quigley and his co-workers [*10,13–16*] and are briefly reviewed:

The effect of the physical presence of balloons in the gut: The presence of a balloon, especially a large one, is unphysiologic, as it acts as a foreign body. Distention by the balloon often induces activity so that the recorded motility is induced rather than spontaneous [*10*]. To quote one example, moderate distention of the colon in dogs, which occurred while obtaining balloon records, was followed by augmentation of tone and activity [*17*]. The balloon, if inflated enough (above 10 cm. of water pressure), may interfere with venous return in the stretched area and simulate obstruction of the digestive tract [*10*].

When a segment of the gut overlying a balloon contracts, the contents of the balloon remain in that segment and offer a greater resistance to the contracting segment than that encountered under natural conditions. Thus the pressures recorded by the balloon system may be gross exaggerations of intraluminal pressures developed under normal circumstances without the physical presence of a foreign body [*18*]. Pressures recorded from a balloon have been found to be two to three times those recorded from a physically accurate recording device fastened adjacent to it [*13*].

Effect of elasticity of the balloon wall: When a balloon is stretched in the alimentary canal the elasticity of the balloon wall makes some contribution to the pressure recorded [*9,10*].

Effect of variations in balloon size, shape, volume and intra-balloon pressure on the pressures recorded: There has been no uniformity in the sizes, shapes and volumes of balloons used by different workers. Also, various workers distended their balloons to different pressures. Table 1 gives the sizes of balloons and the intra-balloon pressures used by past workers. It is obvious that various workers used balloons of any size conveniently available and inflated them to arbitrarily determined pressures.

As a result of experimental studies in the dog, Gruber and De Note [*29*] found that with increase in the size of the balloon the rate of rhythmic contraction in the small intestine was increased, e.g., with a balloon 12 cm. long the rate was much higher than with balloons 2 or 5 cm. long. Also, with the use of long balloons the true amplitude of the contraction was not recorded, because only part of the balloon lay within the contracting segment of the bowel whereas the rest lay in a relaxed portion of the gut and the contents of the balloon from the constricted portion were forced into the portion lying in the relaxed gut. Thus, only a small contraction was recorded when a large one had occurred.

With increase in intraballoon pressure there was an increase in the rate of rhythmic contractions. The peristaltic waves were found to be of increased amplitude when the intraballoon pressure was raised from 15 to 30 cm. of water. Such an increase of pressure induced peristaltic waves if they were not already present, and when the increase in pressure was maintained the waves became progressively less frequent, often dying out altogether.

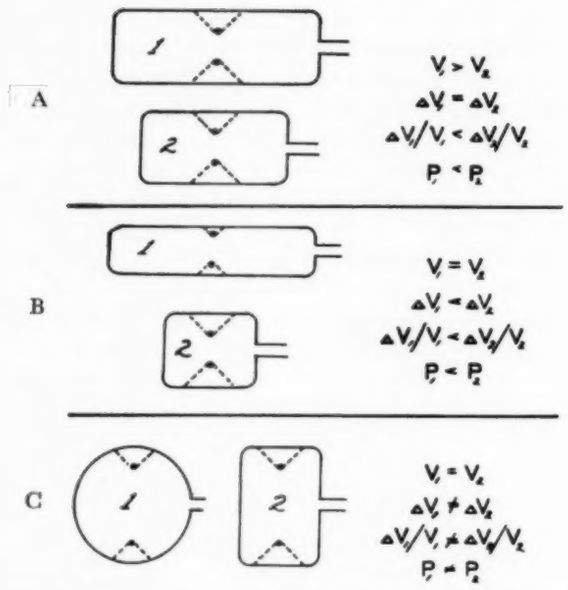

FIG. 1. Illustration of how the size and shape of a balloon influence the pressure recorded by it. From: BRODY, D. A., WERLE, J. M., MESCHAM, I. and QUIGLEY, J. P. *Am. J. Physiol.*, 130: 791, 1940.

Quigley [*14*] has offered evidence to show that pressures recorded from balloons depend on their sizes, shapes and volumes. It is assumed that all the balloons illustrated (Fig. 1) are connected to manometers having identical volume-pressure coefficients.

A represents two cylindrical balloons whose diameters are equal, but the first is longer than the second. Thus the volume of the first is greater than the volume of the second ($V_1 > V_2$). If identical constricting rings are applied to each balloon, identical volume changes are produced.

$$(\Delta V_1 = \Delta V_2)$$

But the ratio of volume change to the original volume will be less in the first than in the second ($\Delta V_1/V_1 < \Delta V_2/V_2$). Since pressure change is directly proportional to the ratio $\Delta V/V$, the pressure created in the first balloon will be less than that produced in the second ($P_1 < P_2$).

B represents two balloons of equal volume but the diameter of the second exceeds that of the first. When identical rings are applied to both,

$$V_1 = V_2$$
$$\Delta V_1 < \Delta V_2$$
$$\Delta V_1/V_1 < \Delta V_2/V_2$$
$$\therefore P_1 < P_2$$

C represents two balloons of equal volume and diameter but the first is spherical and the second is cylindrical. When identical constricting rings are applied to each, there is no reason to anticipate equal changes in volume

$$V_1 = V_2$$
$$\Delta V_1 \neq \Delta V_2$$
$$\Delta V_1/V_1 \neq \Delta V_2/V_2$$
$$\therefore P_1 \neq P_2$$

In view of these considerations it is difficult to accept the accuracy of any quantitative results obtained by the balloon technic.

Difficulty of devising a suitable balloon-manometer recording outfit: Many kinds of pressure-recording devices have been used along with balloons. All of them require a change in balloon volume and in intraballoon pressure to drive them. The volume of gas or liquid displaced from the balloon at different pressures, when connected to the manometer, is of great importance. If the

TABLE 1

Name	Size of Balloons	Amount of Water or Air in Balloons	Intraballoon Pressure
Hines et al. [*19*]	12 cm. by 2.5 cm.	150 cc. of water	...
Jackman and Bargen [*20*]	Varying sizes	Usually 8 to 15 cc. of water; quantity depended on size of balloon	...
Adler et al. [*21–23*]	10 cm. by 4 cm.	...	...
Posey et al. [*24*]	3.5 cm. long	20 cc. of water	18 cm. of water
Hightower et al. [*25*]	5 cm. by 3 cm.	22 cc. of water	...
Chapman et al. [*26*]	6.25 cm. long	20 cc. of air	...
Kern et al. [*27*]	10 cm. long	50 to 75 cc. of air	...
Spriggs et al. [*28*]	4.5 cm. by 3 cm.	About 20 cc. of water; exact quantity depended on capacity of bowel	...
Code et al. [*9*]	5 cm. by 3 cm.	...	15 cm. of water

system is such that the balloon is easily compressed, the balloon may be emptied before the maximal pressure produced by a contraction is recorded. On the other hand, if the system is too rigid and the balloon is filled with liquid, the balloon may be transformed into a hard, incompressible object resembling a golf ball, the presence of which may act as a stimulus to the bowel or may result in the development of excessive pressures when the bowel contracts. Ideally, the volume of liquid displaced from the balloon at a given pressure should be the same as that which would be moved by a contraction of a segment of the bowel which produced exactly the same pressure. This volume-pressure relationship of the bowel is not known, hence the difficulty of devising a suitable balloon recording system [*9*].

High volume pressure coefficients of balloon outfits: Many studies in animals have been made by means of balloons connected to water manometers [*30–32*]. The same device has been used in a number of studies on man [*21–23,27*]. Such systems suffer from all the disadvantages of the balloon technic and also have a high volume-pressure coefficient. The volume-pressure coefficient of a recording device is the ratio of the change in volume at the end inside the gut to the pressure recorded by the manometer. A large change in the volume of the balloon is necessary for recording pressure over a small range. Therefore, when such a system with a high volume-pressure coefficient is used the balloon must contain a large volume; otherwise displacement of the entire contents may be insufficient to record the pressures developed in the gut. This necessarily entails the use of a large balloon which acts as a foreign body. With such a system a complex of pressure and volume changes within the gut segment is recorded which cannot be interpreted with accuracy [*10,14*]. Some workers have used balloons coupled to optical manometers [*24,25,28,33*]. While improving the pressure-registering component of their system, they have continued the use of balloons.

Inaccuracy of pressures recorded: A balloon water manometer or a balloon optical manometer device is not capable of measuring accurately the pressures developed as a result of movements in the alimentary tract. Such records do not merit quantitative analysis. It is inconceivable that such devices are capable of a linear response when registering pressures at different levels. However, Spriggs et al. [*28*] recorded distal colonic activity by means of balloons and an optical manometer and presented the heights of different types of waves in terms of centimetres of water pressure.

Despite these numerous objections to the use of balloons, their use is still being advocated. Code and his co-workers [*9*] point out that the balloon technic is a simple and inexpensive method of detecting motor activity in the alimentary canal and the records obtained by it are sufficient for many research and clinical purposes. They also believe that many of the disadvantages can be avoided or minimised by the use of small balloons (3 by 5 cm.), filled to 15 cm. water pressure, which do not stretch the gut. Bachrach et al. [*34*] maintain that the fact that balloons do not record intraluminal pressures accurately is of no consequence when motility only is being recorded, because the study of gastrointestinal motility is usually concerned with relative rather than absolute effects.

In this review it will be taken that balloons are not suitable for the accurate recording of gastrointestinal motility.

Intraluminal Pressure Recording Technics. Use of open ended tubes: The apparatus consists essentially of narrow tubes filled with gas or liquid whose open ends are introduced into the alimentary canal. (Fig. 2.) The other ends are then connected to suitable manometers. Changes of pressure are transmitted along the column of gas or liquid to a recording device. Schreiber [*35*] was probably the first to record motility from a simple open-ended tube placed in the gut and connected to a water manometer. Templeton [*36*] recorded motility of the empty stomach of dog by this method in 1928.

In 1940 Brody and his co-workers [*13*] were the first to advocate the use of this principle for the study of gastrointestinal motility. They used an air-filled lead and rubber tube 1 mm. in diameter with a tip made of cellulose acetate 2 cm. long and 4 mm. in internal diameter. The tube was connected to an optical manometer. Later, Brody and Quigley [*16*] used 0.4 mm. bore tubing coupled to an electromanometer. Rowlands et al. [*37*] used a modification of Quigley's system. Davidson et al. [*38,39*] recorded mobility from the distal colon of children by means of saline-filled polythene tubes 2.69 mm. in internal diameter, connected to a capacitance-type electromanometer.

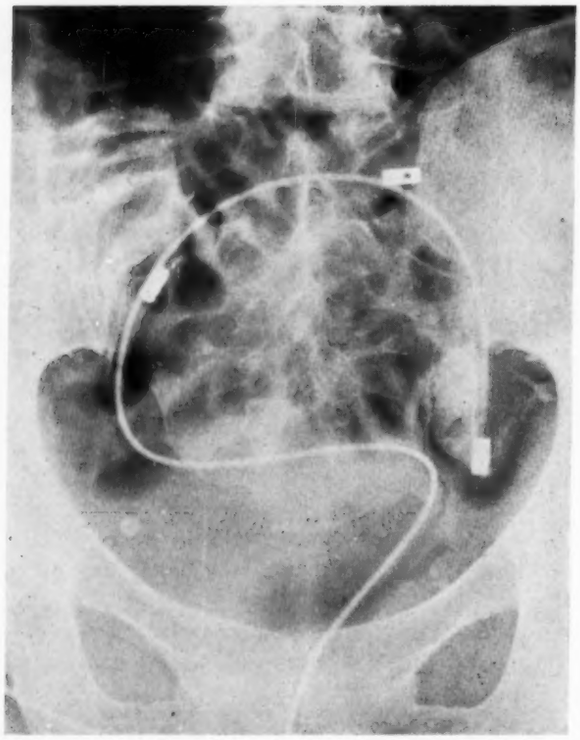

FIG. 2. Showing the use of three open-ended polythene tubes inserted into the lower colon for the registration of intraluminal pressures. One tube (the one furthest inserted) has been filled with a radiopaque medium to demonstrate its position, while the ends of the other two tubes are shown by their terminal metal cuffs appearing as radiopaque rectangles alongside the first tube. From: CHAUDHARY, N. A. and TRUELOVE, S. C. *Gastroenterology*, 40: 1, 1961 [*41*].

Plugging of tubes by gastrointestinal contents is avoided by allowing a steady flow of air (3 to 5 cc. per hour) in the case of air-filled tubes and a steady or intermittent flow of liquid in the case of water-filled tubes [*38–40*].

The use of the open-ended tubes coupled to manometers capable of giving a stable and linear record has many advantages: (1) The small-bore tube has no distending effect on the gut and the effect of the recording tip as a foreign body is minimal [*13*]. (2) Changes of pressure are recorded accurately. Quantitative analysis and comparison of results is made possible, as absolute values are obtained [*40*]. (3) Rapid changes of pressure can be recorded. The balloon technic is not capable of recording changes with a frequency of more than 5 to 9 per minute [*9,40*]. (4) Pressures can be recorded over a wider range than is possible by the balloon-manometer technic [*40*]. (5) Pressure changes which can be interpreted easily are recorded whereas with the balloon technic a complex of pressure and volume change is recorded which is incapable of easy interpretation. (6) Movements of gut contents are not interfered with whereas a balloon hinders passage of intestinal contents [*40*]. (7) A tube remains undisturbed while a balloon is likely to be moved by a powerful contraction [*40*]. (8) Errors arising out of the use of balloons of various shapes, sizes and volumes, which are filled to different pressures, are avoided.

It is plain that by using open-ended tubes filled with fluid, all the advantages of the balloon method are retained while all the disadantages are avoided or minimised.

Electromagnetic transducers: These are potentially useful instruments for recording gastrointestinal motility but they have not been adequately developed for this specific purpose.

The radiotelemetering capsule: This has some advantages but also suffers from certain drawbacks. It causes no discomfort to the patient and allows continuous or intermittent records to be made for up to twenty-four hours. It allows recording of motility from relatively inaccessible regions such as the distal small intestine and the proximal colon in the intact animal or man. Its main drawback is that no means are available for fixing the capsule at one spot, and activity of the same segment or two adjacent segments is not studied with any certainty for any definite length of time because the capsule moves intermittently down the gastrointestinal tract. There is also the possibility of the capsule being arrested by functional or anatomic narrowing of the gut, with undesirable consequences in human subjects at least.

Pressure Recording Devices. Almost all early work on gastrointestinal motility was performed with water manometers. Later, optical manometers and electromanometers came into use. Each of these devices will be briefly considered.

The water manometer: This is now an obsolete instrument and its use has many drawbacks [*16*]. It is too sluggish in dynamic response to permit faithful registration of movements. It also has a high volume-pressure coefficient and may only permit registration of the lower portion of a pressure change. A typical water manometer employed for gastrointestinal motility investigation required a volume change of 0.5 ml. for every 1 cm. of water pressure recorded. Such a manometer recording from a cavity with a volume of 5 ml. would not record a pressure more

than 10 cm. of water [*14*]. With adequate equipment it was possible to record pressures exceeding 100 cm. from a gut segment having a volume less than 5 cc. [*10*]. Another drawback is that much attention is required for the apparatus and there are many sources of malfunction if multiple simultaneous records are to be obtained.

Optical manometers: An optical manometer consists essentially of a mirror mounted on a sensitive membrane; this mirror reflects a beam of light on continuously moving photographic paper. Pressure variations cause movement of the membrane which results in movement of the reflected beam. These are useful devices and a great deal of work has been performed with them. They are simple in construction, stable in operation and low in cost. The only drawback is that the photographic records need to be developed and if prolonged observations, such as are necessary in gastrointestinal motility studies, are to be made, much time and effort is needed to develop the records.

Opticoelectrical systems: As in the purely optical systems, detection of the movement of the membrane takes place by means of a mirror which reflects an incident beam of light. Instead of falling on the photographic paper, the light falls on a photo cell which receives a varying proportion of the light, depending on the movement of the mirror. These variations are transformed into electrical variations and conveyed to amplifiers. This is the principle employed in the Cambridge 3-channel Recorder which has been used in our own studies [*41–43*].

Electromanometers: In such devices the movements of the manometer membrane are transformed into electrical energy which is then transferred to the ultimate recorder. The transformation of the pressure impulse may be effected according to different principles, e.g., changes of ohmic resistance, piezo-electrical effect, induction phenomena and changes of capacitance. Electromanometers are, on the whole, fairly useful instruments, but most of them are inferior to the best of the optical manometers [*44*].

RESULTS IN ANIMALS

The first important study was made by Bayliss and Starling [*45*] who recorded motility by means of balloons inserted into the denervated and isolated saline-immersed colon of the dog. The animals were given a dose of castor oil on the previous evening and morphia as an anaesthetic. Bayliss and Starling described two types of contractions: (1) rhythmic contractions starting above the balloon and appearing to travel downwards, each lasting ten to forty seconds; and (2) smaller, irregularly occurring contractions lasting two to four seconds, superimposed on the rhythmic contractions. They noticed extreme variations in colonic activity; sometimes the colon was in a state of tonic contraction, at other times it was completely relaxed. They also described two local reflexes: (1) *Descending inhibition:* A stimulus, e.g., a pinch applied to any part of the colon or even to the lower part of the ileum, at once produced complete inhibition of the whole colon below the stimulated point. The same inhibitory effect was observed below a descending peristaltic wave. (2) *Ascending excitation:* In some instances, pinching the intestine half an inch below the balloon evoked contraction over the balloon.

Cannon [*46*] studied the movements of the colon of the cat by roentgenograms. According to him the usual movement of the caecum, ascending colon and transverse colon was an antiperistalsis. This recurred in periods of about five minutes each, every fifteen minutes or so. During each period waves recurred at a rate of about eleven waves in two minutes. The sequence of events in the colon was as follows: (1) when food entered the large intestine, a strong, general contraction took place along the caecum and ascending colon, forcing some of the food onwards; (2) a little later antiperistaltic waves occurred in the same area; (3) when material accumulated in the transverse colon, deep tonic constrictions appeared one after another and carried the material into the descending colon, leaving the transverse and ascending portions free for antiperistaltic waves; (4) in emptying the large intestine, most of the material in the lower descending colon was voided by peristaltic waves and the pressure of abdominal muscles, the peristaltic waves then pushed the remaining faeces into the lower descending colon which was emptied once again.

Emotional factors such as fear, stress or rage were accompanied by a total cessation of movement. Movements continued during sleep and at night.

Elliott and Barclay Smith [*1*] studied the movements of the large intestine in a variety of animals. The colon was directly examined while floating in a bath of warm saline solution. The

animals were under ether anaesthesia, their spinal cords having been destroyed below the fifth or sixth thoracic segments. The stimulus to movement was the distention produced by driving gruel through the gut. They concluded that there were three usual forms of muscular movement in the colon, which justified a division into three functional segments, each segment being distinguished by the predominance of one or other of these movements. They also considered this concept in relation to the human colon.

(1) Backward running waves which started from the lower end of a distended area and were churning in function. These constituted the main activity of the proximal colon. The proximal colon in these animals corresponded to the caecum and ascending colon in man, where food coming from the ileum was delayed and mixed by a backward current.

(2) Coordinated peristaltic waves which drove the food in only one direction, i.e., towards the anus, and were present throughout the colon but were the sole movement of the middle portion. This middle portion in animals corresponded to the transverse and descending colon in man, where propulsive peristalsis was thought to be the major activity.

(3) Powerful, slow constrictions starting at a definite point some distance up the colon and spreading downwards to empty the distal portion. This was the main activity of the distal colon of animals, which corresponded to the sigmoid colon and rectum of man.

Welch and Plant [*30*] studied the activity of the colon of the dog by means of balloons inserted into the lumen. According to them the normal activity of the dog's colon was irregular and consisted of marked variations of tone, with or without superimposed contractions which occurred most frequently when the tone was high. Periods of high tone recurred at regular intervals of fifteen to thirty minutes and lasted for five to fifteen minutes. Activity varied from almost continuous high tone with short periods of relaxation to long periods of inactivity with short infrequent contractions.

Templeton and Lawson [*31*] studied the colonic motility of dogs with caecostomies. One set of three balloons was inserted through the caecostomy and another similar set through the anus, so that balloons I, II, III, IV, V and VI came to lie at the ileocaecal junction, the middle of the transverse colon, the splenic flexure, the descending colon, the sigmoid colon and the rectum, respectively. This enabled them to compare the activity of the proximal and distal portions of the colon. They described three types of contractions which occurred in the proximal and the distal colon.

Type I contractions: These were rapid contractions which appeared on the tracing as single curves, often superimposed on type II contractions, usually occurring simultaneously at the levels of different balloons, although frequently a type I contraction appearing at the level of one balloon could not be found at the level of another balloon. They never appeared with progressive delay at the levels of contiguous balloons; in other words, they were not propulsive waves.

Type II contractions: These were slower contractions surmounted by the more rapid type I contractions. They were often observed to occur simultaneously at the levels of contiguous balloons or with progressive delay oralwards or towards the anus. Thus, sometimes these were simultaneous waves and at other times they were modified to produce a peristaltic or antiperistaltic effect.

Type III contractions: These were changes of tonus surmounted by type II contractions.

Templeton and Lawson [*31*] were not sure whether type I and type II waves were separate entities or different forms of the same wave. In their opinion, the existence of progressively delayed type II contractions, but the invariable simultaneous occurrence of type I contractions, justified their being considered different types of waves. On the other hand, the fact that larger type II contractions frequently followed a period of smaller type I contractions and increased in amplitude as the type I contractions decreased, suggested that type II waves were produced by the summation of type I waves; the manner of summation with repression of one or more of the type I contractions determining the direction of passage of type II waves in contiguous areas. Also, in the production of progressively delayed type II contractions the delay was found to be equal in duration to one or an integral multiple of a type I contraction and one or more type I components seemed to be omitted.

Templeton and Lawson found differences in the activity of the proximal and the distal colon. In the proximal colon, activity was periodic; periods of increase in tone with superimposed type I and type II contractions alternating with periods of almost complete quiescence. In the

distal colon, i.e., from the splenic flexure to the anus, changes in tone were less pronounced; the usual changes being sudden depressions in tone with a gradual return to a former or a higher level. Type I and type II contractions were of lower amplitude and were more regular in height and rate of occurrence. Progressively delayed type II contractions were less frequent. There was often an abrupt change in the type of activity at the splenic flexure; a sharp depression of tone and activity in the distal colon often coincided with a rise of tone and increase in activity in the proximal colon, and vice versa. However, rhythmic type I and type II contractions frequently occurred throughout the entire colon, or in one segment without affecting the activity of the other segment. In the distal colon this rhythmic activity was the one usually encountered, although occasionally there was complete quiescence, with proximal colon activity extending into it for variable distances.

Larsen and Bargen [*32*] recorded the motilty of the colon in the dog with a set of three balloons. The first balloon was in the caecum, the second was near the splenic flexure, the third was in the lower sigmoid colon. They found the colon of the dog to be quiescent most of the time and recorded activity that was similar to the descriptions of earlier authors only when the gut was stimulated by overdistention of the colon.

Large tonic waves, variable in amplitude and duration, appearing six to eight times in one hour, each lasting for about five minutes. These were less pronounced and less frequent in the distal colon than in the proximal colon.

Small tonic waves which surmounted the large tonic waves and occurred at a rate of five to six waves in four minutes. These often occurred independently in the proximal and distal portions of the colon, although occasionally they could be followed from one balloon to the next with a delay of ten to fifteen seconds between two waves. Usually they occurred with progressive delay analwards, but rarely they seemed to travel orally.

Short rapid waves which surmounted the small tonic waves and occurred at a rate of eight to ten waves per minute. These seemed to be the only movements present normally in the colon. They were almost always in evidence and were uniform in amplitude and duration. They occurred simultaneously or independently in different segments of the gut, but never with progressive delay. They were encountered more often in the caecum than in the distal parts of the colon. In addition to these waves Larsen and Bargen observed a pulsating type of wave in which the entire organ contracted as a single unit. This was seen more often than the other kinds of waves.

Raiford and Mulinos [*4*] studied the movements of segments of the colon of the dog. These segments, which were 8 to 10 cm. long, were exteriorised, opened longitudinally or transversely, and connected to a recording mechanism. The usual resting pattern of activity as observed by them consisted of rhythmic contractions which were more marked in the circular muscle and occurred at intervals of thirty to sixty seconds. These rhythmic contractions lasted for up to two hours.

Regan and Puestow [*47*] made naked eye observations of segments of the colon of the dog, which were transplanted on the anterior abdominal wall. They described three types of contractions.

Type I contractions: These were small localised contractions involving only a portion of the circumference of the segment, producing a faint surface dimpling, and did not progress up or down the segment. These waves started slowly one to two minutes apart and increased in frequency until they occurred at a rate of three per minute. They continued at this rate for two to four minutes and then slowly subsided. They were observed more often in the proximal colon.

Type II contractions: These were deeper contractions seen as distinct circular indentations, which started at the proximal end of the segment and progressed to the distal end. They generally but not invariably followed a few type I contractions and were often interspersed with them. They occurred every fifteen to thirty minutes in the ascending colon, every twenty to forty minutes in the transverse colon, and less frequently in the lower descending and sigmoid colon.

Type III contractions: These were contractions involving the entire segment at the same time, often occurring independently of type I and type II contractions. They were produced by contraction of the circular and longitudinal muscles, separately or together. These waves did not occur at a regular rate; sometimes they were encountered two to three times in three hours and at other times they were not seen at all during a similar period. In fact, they occurred so infrequently that Regan and Puestow in-

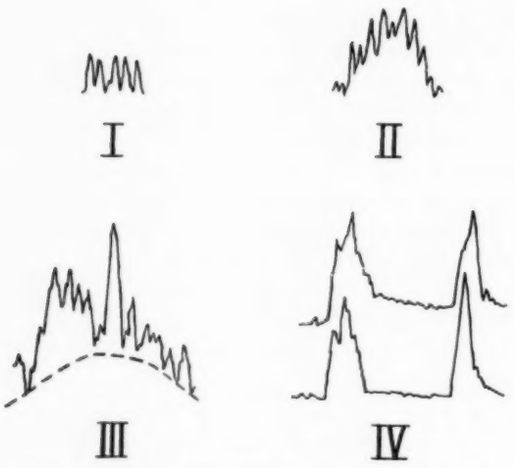

FIG. 3. Diagrammatic representation of the types of wave recorded in earlier studies of colonic motility, based on the observations of Adler et al. [*21*], Spriggs et al. [*28*] and Kern et al. [*27*].

cluded them among the normal movements of the colon only after observing them following the administration of morphine, prostigmine or 20 per cent saline solution.

Studies were also made by Currie and Henderson [*48*] in the guinea pig, and by Barcroft and Steggarda [*49*] in the dog. These, however, did not add much to what was observed by workers whose studies have been reviewed in the preceding pages.

RESULTS IN MAN

Apart from some roentgenologic studies [*50–53*], the first systematic study of human colonic motility was probably that made by Adler, Atkinson and Ivy [*21*]. They studied the motility patterns of the proximal descending colon in four men with colostomies, by means of balloons and water manometers. Posey et al. [*24*] recorded the motility of the proximal colon in four subjects through stomas in the transverse colon, and the motility of the sigmoid colon in a number of other subjects by means of rubber balloons connected to optical manometers. Posey and Bargen [*33*] recorded motility by the same technic in twenty-four patients with ileac or colonic stomas. Spriggs and his coworkers [*28*] recorded motility patterns from the pelvic colon and rectum of ten normal persons and ten patients with ulcerative colitis by means of balloons and optical manometers.

Grace, Wolf and Wolff [*3*] made naked eye observations of prolapsed segments of the colon in four subjects with colostomies. Two of these subjects had colostomies because of ulcerative colitis which they had had for many years; the remaining two had colostomies because of rectal strictures due to lymphogranuloma venereum and diverticulitis, respectively. The most frequent movement observed was a localised circular constriction, usually involving less than 25 mm. of the exposed segment of the colon. The constriction began slowly, reaching its peak in thirty seconds, and gradually disappeared. This type of constriction was often deep enough to divide the exposed bowel into two parts. Generally, such activity occurred every ten to fifteen minutes. Occasionally, when areas of localised constriction persisted, a second type of contractile activity was seen. This was characterised by radiation of waves from the contracting caudal end with general constriction and shortening of the long axis of the bowel by as much as 50 per cent. Usually two to three minutes elapsed from the beginning to the end of such a constriction. These constrictions were seen every fifteen to twenty minutes. It must be remarked that to base any general conclusions about normal colonic motility on the behaviour of prolapsed segments of colon appears to us to be most unwise.

Types of Wave in Normal Subjects at Rest. Adler and his co-workers [*21*] described the occurrence of three types of waves (type I, type II and type III) in the human colon. (Fig. 3.) Posey et al. [*24*], Posey and Bargen [*33*], Spriggs et al. [*28*] and Code et al. [*9*] were in general agreement with Adler, Atkinson and Ivy. Their description of the different types of wave was as follows:

Type I waves: These were simple and small waves which had a mean duration of five seconds and a mean pressure of 6.8 cm. of water when recorded from the pelvic colon [*28*]. When such waves were recorded from higher regions in the colon they often lasted longer and were of greater amplitude. Their duration, however, seldom exceeded twelve seconds and their amplitude was usually not more than 12 cm. of water [*9*]. When rhythmic, their rate in the pelvic colon was about thirteen per minute [*9*], whereas in the descending colon it ranged from three to eight per minute with a mean of six per minute [*21*]. Throughout the colon they were often superimposed on type II and type III waves and occurred only occasionally in the pure form, when the colon was in a state of low tone [*24*]. However, they were not seen frequently in recordings from the lowest part of the large

bowel, and occurred during only 1.1 per cent of the total time of observation in records from the pelvic colon. This part of the large bowel was active for 36.6 per cent of the total time of observation in healthy subjects [*28*].

As regards the significance of these type I waves, all these workers agreed that they were non-propulsive. They had never been recognised by direct observation or roentgenologic examination of the human colon [*9*]. According to Posey and Bargen [*33*] they represented the haustral activity of the colon, but no reason was advanced by them in favour of this view. However, they also stated that type I waves were intensified by the presence of balloons in the colon and were in all probability initiated by the balloon system. They were also not sure as to whether such activity differed markedly from that occurring in a bowel containing faecal matter.

Type II waves: A typical type II wave was a rise of baseline pressure with superimposed type I contractions, which gave the appearance of a "Christmas Tree" wave [*9*]. According to Posey et al. [*24*] they had a duration of 45 to 120 seconds, but according to Spriggs and his coworkers [*28*] they lasted for twelve to sixty seconds, with a mean duration of twenty-five to thirty seconds. When rhythmic, they occurred at a rate of two waves per minute. Their mean amplitude when recorded from the pelvic colon was 9.7 cm. of water although occasionally waves with a height of 50 cm. of water were seen [*28*]. In another study their mean amplitude was found to be 6.5 cm. of water [*9*]. In the descending colon, type II contractions were on the average twice as high as the type II contractions in the pelvic colon. These waves comprised the major activity seen in records from the proximal part of the descending colon and the pelvic colon. They were present 36.3 per cent of the time of observation in the pelvic colon, total activity being present 36.6 per cent of the time [*21,28*].

Type II waves occurred independently or simultaneously in adjacent segments of the gut. They could be propulsive or non-propulsive. Their propulsive nature was evidenced by the fact that transport of bowel contents was never observed in their absence, although in the majority of cases they did not induce transport. Propulsion depended on the amplitude of type II contractions and the relation of such contractions to one another in adjacent segments. Contractions of low amplitude which were not perceived by the highly trained subjects of Adler et al. were non-propulsive, whereas contractions of a higher amplitude were perceived as a sensation of "about to expel contents" and were propulsive [*21,24*].

Adler, Atkinson and Ivy [*22,23*] developed the concept of "functional segmental motor activity" and of coordinate activity between adjacent segments of the bowel. When balloons 3 cm. long were placed 7 cm. apart, they showed separate types of activity, but if placed nearer each other the activity was the same. Therefore, they divided the colon into functional units. Two adjacent segments represented a coordinated functional unit when a type II contraction occurred in a proximal segment and was followed by a similar contraction in the distal segment, leading to the propulsion of contents. If a type II contraction in the proximal segment was not integrated or coordinated but was disorganised in relation to the activity in the distal segment, no propulsion could take place. A major portion of colonic activity was found to be of the incoordinate type. In short, two or more segments could represent a functional unit; when mass peristalsis occurred, as in defaecation, the entire colon behaved as a functional unit. However, their articles do not contain any records showing this type of progressive and coordinated segmental activity.

Posey and Bargen [*33*] subscribed to the same concept and emphasised the importance of the physiologic block exerted by each functional segment on its immediately proximal neighbor. According to them, the process of intersegmental incoordination prevented the too rapid transport of material down the intestinal tract.

McMahon and his group [*54*] also divided type II waves into coordinated and incoordinated types, but Code et al. [*9*], working in the same laboratory, found on re-examination of the records that waves tabulated as coordinated type II contractions occurred simultaneously on both balloons of the tandem system and therefore did not represent activity initiated in the proximal segment and passing to the distal segment. However, Code e al. [*9*] do not favour abandonment of the concept of coordinated type II waves and they suggest that these waves could be the most important type of activity of the proximal colon.

Spriggs et al. [*28*] and Code et al. [*9*] believed that type II contractions represented the

haustral activity seen by roentgenologists, as there was already evidence that haustral contractions were not propulsive peristaltic waves but had a mixing function. The concomitant disappearance of haustra and the diminution of type II activity in cases of ulcerative colitis has also been cited as supporting the belief that type II waves represented haustral activity [*28*].

To summarise, Spriggs et al. [*28*] and Code et al. [*9*] assigned a mixing function to type II waves whereas Adler et al. [*21*] and Posey and Bargen [*33*] thought the coordinated type II waves to be peristaltic but did not suggest any function for the simultaneous type II waves.

Type III waves: These were described by Adler et al. [*21*] as waves of complex pattern composed of a change in baseline pressure or in tonus on which were superimposed either type I or type II waves or both. According to Posey et al. [*24*] they lasted one to fifteen minutes, the majority lasting for about five minutes; but according to Code et al. [*9*] they lasted one to four minutes. They occurred only 2.3 per cent of the total time of observation [*28*]. A pressure rise of 3 to 5 cm. of water in the pelvic colon [*28*] and 8 to 10 cm. of water in the descending colon [*9*] has been described.

The type III waves have not been seen by roentgenologists [*9*]. The small amount and slow rate of change of pressure associated with them would render them almost imperceptible by single or serial x-ray examination. These waves were not propulsive in themselves, and if propulsion did occur, it was due to superimposed type II contractions [*22,24,27*]. Their prolonged duration suggested that perhaps they aided absorption by increasing the hydrostatic pressure in the gut [*55*], but little other evidence supported such a hypothesis except that they did not seem to be associated with propulsion and were obviously not mixing waves [*9*].

WAVES OBSERVED BY MODERN METHODS OF RECORDING

Davidson and his group [*38*] recorded motility patterns from the distal colon of children by means of open-ended polythene catheters, connected to Sanborn electromanometers. Simultaneous records were made from the sigmoid, rectosigmoid, upper rectum and lower rectum. From the sigmoid and rectosigmoid they recorded practically identical waves of short duration with sharp peaks. From the lower rectum they recorded rounded waves of longer duration, and from the upper rectum they recorded waves resembling at times those recorded from the rectosigmoid and at other times those recorded from the lower rectum. Differences in the motility patterns between the lower rectum, rectosigmoid and sigmoid were analysed by separating waves into divisions of 3 cm. of water pressure for amplitude and ten seconds for duration. The distribution of wave forms for each category was then plotted. The percentage distribution of waves of similar amplitude was identical for all three regions of the colon. More than two-thirds of the waves had an amplitude less than 6 cm. of water. As regards duration, longer waves tended to occur in the rectum.

On analysing their data these workers found no reason for separating waves into type I and type II contractions on the basis of amplitude, as there was no sharp point of separation between small and large waves. However, because of the wide range of duration of waves, they considered waves of long duration to be different from waves of short duration. In their view, this opinion was supported by their finding that waves in the rectum were chiefly of long duration. The fact that some long waves had short waves superimposed on them did not seem to nullify the conclusion. They, therefore, considered the idea of separate type III waves as valid, as they were identical with their own waves of long duration.

They proposed a new nomenclature: "phasic waves," waves of short duration; and "tonus waves," waves of long duration or rises in baseline pressure.

None of the wave forms appeared to be peristaltic. For the most part, waves of short duration (corresponding to types I and II in the older nomenclature) occurred simultaneously in different areas whereas waves of long duration occurred independently in one segment at a time.

Chaudhary and Truelove [*41*] found that the majority of the waves recorded from normal subjects were simple waves, and almost always represented positive changes in pressure. (Fig. 4.) These simple waves assumed two main forms, although every intermediate stage was seen. The first form was when the wave consisted of a small rise of pressure (2 to 5 mm. Hg) with a gentle rise to its peak and an equally gentle decline to the original level, the duration of the complete wave being ten to thirty seconds. The second form differed from the type just described in showing a steeper rise of pressure with a bigger amplitude (10 to 20 mm. Hg) and a sharper

descent to the original pressure, the duration being ten to thirty seconds. The smaller specimens of these simple waves corresponded in size and form to the type I waves described in the early literature, but type I waves are said to occur as only a small fraction of the total waves at rest, whereas in the study of Chaudhary and Truelove these simple waves as a whole were the main form of motor activity recorded.

Exceptionally, some of these simple waves were negative, although in other respects conforming to the general description given. In one subject a series of these negative waves occurred in what appeared to be a rhythmic sequence.

Occasionally, complex waves occurred, with small waves repeatedly superimposed on a primary rise and fall of pressure. These complex waves appeared to correspond to the type II waves recorded in the literature but in this study they were unusual findings in subjects at rest whereas they have been said to be by far the most prominent type of wave recorded from the colon. Bigger waves than those so far mentioned were unusual in normal subjects at rest. When seen, they were usually simple waves but were occasionally complex.

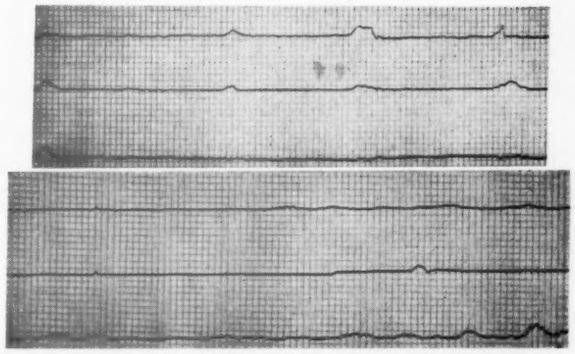

FIG. 4. Typical examples of colonic motility of healthy subjects at rest. Records are taken from two separate subjects. Each record represents six minutes of recording time and the same time-scale is employed in all similar records reproduced in this article. As far as the amplitude of wave is concerned, each clearly defined square on the record represents 10 mm. Hg; the same pressure scale is employed in all subsequent records reproduced in this article.

EXTENT TO WHICH THE COLON WAS ACTIVE OR QUIESCENT

Adler and his co-workers [*21*] found that the degree of motility varied from one subject to another. Colonic activity was consistently more marked in one subject than in the others, being present for 70 per cent of the time of observation as compared to activity for 54, 46 and 41 per cent of the time, respectively, in the other three. In all of them, colonic activity could be either simultaneous or independent in adjacent segments and was subject to sudden variations without any apparent cause. Periods of quiescence for as long as sixty minutes and periods of continuous activity lasting up to 180 minutes were observed. Posey et al. [*27*], Posey and Bargen [*33*], and Davidson et al. [*38*] all found that periods of quiescence alternated with periods of activity.

RESTING PATTERNS IN NORMAL SUBJECTS

Chaudhary and Truelove [*41*] found that the usual pattern consisted of irregular periods of activity. A period of activity might consist of a single wave or of a series of waves, varying from two to three to a larger number. Activity at one level in the gut was often independent of the state of activity at the other levels. For example, if the gut at the level of one of the tips was exhibiting motility, there was often complete quiescence at the levels of the other two tips, or two might be active and the other inactive; sometimes the gut was active at all three levels. When colonic activity was being registered by more than one tip, the waves recorded from one tip usually bore no fixed relationship to the waves recorded from the others. When waves were recorded simultaneously from all three tips they might be closely similar in form or totally different. It was rare to record waves showing progressive delay from tip to tip working analwards. In occasional subjects, little colonic activity was recorded during the whole course of basal recording. Even more rarely, a period of almost continuous rhythmic activity was registered by one or more of the pens.

There was considerable variation among normal subjects in the degree of motor activity recorded by this method over a period of one hour. Some subjects displayed almost complete quiescence of the sigmoid colon, whereas the most active had waves occurring for one-quarter to one-third of the period of observation. The mean period of activity, expressed as a percentage of the total time of observation in which waves were occurring, on an average lead amounted to 12.9 per cent for the group of normal subjects.

MOTILITY PATTERNS IN ULCERATIVE COLITIS

Very few studies have been made of motility patterns in ulcerative colitis. Ganter and

TABLE II

	Type of Wave				
	I	II	III	IV	Total
Normal subjects	1.1	36.3	2.3	0.0	36.6
Patients with ulcerative colitis	2.9	9.8	0.0	8.1	19.0

TABLE III

	No. of Tracings	No. of Patients
No activity	21	16
Greatly reduced activity	23	17
Normal activity	24	17
Increased activity	4	4

Stattmuller [*56*] studied a patient with ulcerative colitis who had a colostomy in the proximal colon. Motility was recorded by means of a single balloon introduced through the stoma. They found high waves occurring in groups; the balloon moved analward each time such a group of waves was recorded. These waves were considered identical with the large contractions described by Holzknecht [*50*].

Posey and Bargen [*33*] recorded the motility from the colonic stomas of two patients with ulcerative colitis by means of balloons and optical manometers. There was almost complete absence of pure type I contractions and complete absence of type III contractions. The single dominant pattern was of type II waves, with complete intersegmental coordination at all times. It was apparent from a study of their motility records that waves in the distal segment followed waves in the proximal segment. The type II waves were rhythmic but not absolutely regular. Peaks were reached every two and a half to four and a half minutes. There was constant hypermotility, with no quiet or even relatively quiet intervals. The diarrhoea was thought to be due to excessive intersegmental coordination with deficient or absent physiologic blocking in the face of constant hypermotility. In one of the two patients studied through an ileac stoma following colectomy the same motor disturbance was observed in the small bowel.

Spriggs and his co-workers [*28*] compared the motility of the pelvic colon and rectum of ten normal persons with that of ten patients with ulcerative colitis. The duration of illness ranged from two months to five years, and all patients had ulcerative colitis of some severity, with inflammation of the rectum and sigmoid colon. They used water-filled rubber balloons together with optical manometers. One balloon was 18 cm. from the anal margin while the other was at a distance of 8 cm. They observed that patients with ulcerative colitis gave the impression of a less active pelvic colon. Activity was present for 19 per cent of the total time of observation as compared to 36.6 per cent of the time in normal subjects. The most noticeable reduction was in type II activity. This was present for 9.8 per cent of the total time of recording in patients with ulcerative colitis as compared to 36.3 per cent of the time in normal subjects. Occasionally, although not in every patient, a new type of wave called a type IV wave was observed. It was usually accompanied by some evidence of propulsion. This wave was encountered 8.1 per cent of the total time of observation in patients with ulcerative colitis and was seen only once in five hours of postprandial observations in normal subjects. The changes in the distribution of different waves, expressed as a percentage of the total time of observation, as observed by Spriggs et al., are shown in Table II. The differences in the colonic activity of the two groups were attributed to the factor of ulcerative colitis.

Kern et al. [*27*] studied the sigmoid motility of forty-five patients with ulcerative colitis by means of balloons and water manometers. In all patients the sigmoid colon was involved, but there were great variations in the severity of the illness as judged by the frequency of bowel movements, other clinical symptoms, and objective changes in the colon. In all, seventy-two tracings were obtained and colonic activity was found to be reduced or entirely absent in forty-four tracings. The results are shown in Table III.

In their opinion, motility records with little or no activity were characteristic of patients with marked diarrhoea. Patients with active disease, as observed through a sigmoidoscope, but with no diarrhoea, had normal motility records, and those with hyperactive tracings were actually constipated. A new type of wave, called a type IV wave, was observed to occur in nine tracings, which otherwise showed a marked diminution

of activity. The reduction in activity was not related to the duration of illness, roentgenological appearance or the degree of fibrosis found after colectomy or autopsy.

Davidson and his group [*39*] studied the motility of seven children with chronic ulcerative colitis, six infants suffering from acute diarrhoea and eleven normal children who were given magnesium sulphate orally. They used saline-filled, open-ended tubes along with capacitance type electromanometers. The children with ulcerative colitis were from five to fourteen years old. Each of them had had the disease for at least one year and all exhibited the characteristic proctoscopic signs. At the time of study three were passing blood in their stools but none were having diarrhoea. No differences were found between the motility patterns of these children and normal children.

In infants with acute diarrhoea the total amount of activity during thirty-minute periods was not reduced as compared to normal children, although fewer waves were recorded. The waves were, however, of higher amplitude (two to three times) and were longer in duration. Activity in all three segments was coordinated, and when the waves reached the lower rectum the child was noted to strain and pass flatus or a small amount of watery stool. This "peristaltic pattern" (as designated by Davidson et al.) was observed in all six infants with diarrhoea. Its frequency of occurrence correlated with the severity of symptoms at the time of study. While plotting the curves for amplitude and duration in such infants it was found that the percentage distribution of wave forms in terms of amplitude coincided in all colonic areas, as in normal children and children with ulcerative colitis who were free from diarrhoea. But, unlike these two groups, the percentage distribution of wave forms in terms of duration coincided for the sigmoid and the rectum; in other words, a greater percentage of waves of longer duration were recorded from the sigmoid colon and the rectosigmoid region. In their opinion the similarity in the amplitudes and durations of waves from different segments in diarrhoea indicated a coordination of these segments in the diarrhoeal state. This wave of high amplitude and long duration seen in children with diarrhoea was called a "propulsive wave" and was considered identical with the type IV wave of Kern et al. [*27*] and Spriggs et al. [*28*].

Fifty per cent solution of magnesium sulphate was administered to eleven normal children in a dose of 1 ml. per kg. body weight. Eight of the eleven children responded by exhibiting motility patterns similar to those noted in infants with diarrhoea. When the characteristic wave appeared, tenesmus or urgency developed. The relative absence of other types of activity, once the large peristaltic waves appeared, was striking.

Chaudhary and Truelove [*41*] made forty-nine separate observations on thirty-six subjects with ulcerative colitis in different stages of the disease. They found that the resting patterns of motility varied according to the clinical stage of the disease. In patients who were suffering at the time of observation from frank, bloody diarrhoea and constitutional disturbances, there were about as many colonic waves per hour as in normal subjects but these waves included a larger proportion of waves of high amplitude and long duration, together with a corresponding reduction in the number of the smaller waves. In patients with mild symptoms there was little difference from normal patterns. The patients who were symptom-free, but with sigmoidoscopic evidence of active disease, showed a definite reduction in total motility. The number of waves was reduced and they were typically of low amplitude but of long duration. Patients who were symptom-free and who also had normal appearances on sigmoidoscopic examination had normal patterns of motility.

Type IV waves (*Fig. 3*)*:* This was described as occurring in patients with ulcerative colitis [*27,28*]. It was a simple wave lasting two to five minutes with a mean duration of 2.2 minutes. It had an amplitude two to three times that of a usual type II wave, and the mean amplitude was 14 cm. of water. When in rhythmic sequence, it occurred at a rate of one wave every two or more minutes. It was not encountered in all patients with the disease [*28*], and was found in only nine of seventy-two observations on forty-five patients with ulcerative colitis [*27*]. It was present only when other kinds of motility were markedly reduced [*27*] and was noted to be present for 8.1 per cent of the total time of observation in ten subjects with ulcerative colitis [*28*]. It had a relatively sharp ascending limb, and a more gentle descending limb. The surface area beneath such a wave was eight times that beneath an average type II contraction [*27*]. According to Kern et al. [*27*] the wave progressed from the proximal balloon to the distal

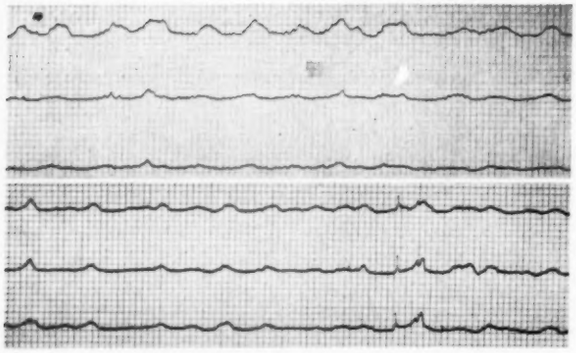

FIG. 5. Typical examples of the resting pattern of colonic motility in patients suffering from spastic colon. The marked hyperactivity is readily appreciated if these records are compared with those of Figure 4.

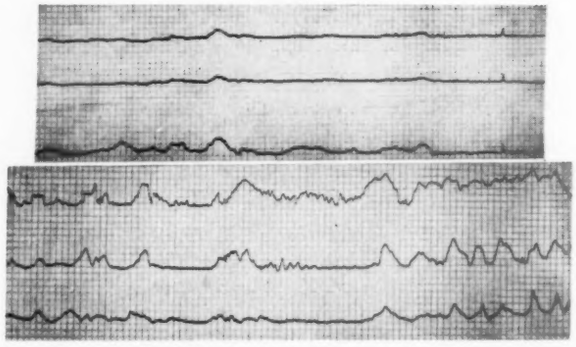

FIG. 6. Typical examples of the patterns of colonic motility after the administration of prostigmine. *Top*, normal subject, whose resting pattern is shown in Figure 4 (upper record). *Bottom*, a patient with the irritable colon syndrome.

balloon 10 cm. away in one minute, but according to Spriggs and his workers the wave was recorded simultaneously from different segments of the gut, every wave in the sigmoid colon being accompanied by a wave in the rectum. Davidson et al. [*39*] believed that their "propulsive waves" seen in patients with acute diarrhoea and after the administration of magnesium sulphate were identical with the type IV waves of Spriggs et al. [*28*] and Kern et al. [*27*]. On some occasions these waves appeared to progress from one segment to another and thus appeared to represent propulsive activity; on other occasions they occurred in contiguous segments at the same time and thus appeared to represent a fairly widespread contraction of the colon; whereas on still other occasions they occurred in an isolated segment only.

Kern et al. [*27*] observed that type IV waves were associated with a feeling of fullness in the rectum and a desire to defecate, and were in fact sometimes accompanied by the passage of flatus, faeces or the lowermost balloon from the rectum. Consequently they decided that type IV waves were identical with the mass movements in the colon described by roentgenologists [*50,52*].

Davidson et al. [*39*] believed that these waves were characteristic of the diarrhoeal state and not of ulcerative colitis *per se*. This belief was based on their findings that these waves were absent in children with ulcerative colitis who were free from diarrhoea at the time of observation, but present in children suffering from diarrhoea due to diverse causes, including ingested magnesium sulphate.

Chaudhary and Truelove [*41*] observed that patients with active ulcerative colitis were much more prone to exhibit large waves of high amplitude and long duration than were normal subjects. They thought it possible that some of these big waves corresponded to the type IV waves of earlier workers [*27,28*].

MOTILITY PATTERNS IN THE IRRITABLE COLON SYNDROME

No systematic studies of the resting patterns of motility found in the group of patients with functional colonic disorders embraced by the term "irritable colon syndrome" were made until Chaudhary and Truelove [*41*] made fifty-seven observations on forty-six patients. The type of motility pattern depended on the clinical type of colonic disturbance and on whether the patient was in a stage of symptoms or not.

Among the patients with colonic pain as a dominant symptom (spastic colon group) it was usual to find considerable hyperactivity in the resting patterns. (Fig. 5.) The hyperactivity consisted of more frequent colonic contractions and especially of large contractions, which were unusual among the normal subjects. Large contractions with an amplitude of more than 30 mm. Hg were ten times as common among the patients with spastic colon as among normal subjects. The resting pattern obtained from such a patient with a spastic colon in a stage of symptoms was conspicuously different from that of a normal subject. However, when these patients had their colonic motility recorded in a symptomless stage there was no appreciable difference between their records and those of the normal group, with the solitary exception that waves bigger than those seen in normal persons were occasionally encountered.

By contrast with the results obtained in the patients with spastic colon, the picture of colonic motility in patients with pure diarrhoea was essentially normal. There was some suggestion that they displayed *less* activity than normal when in a stage of symptoms, but the difference was not a striking one. When symptom-free, they corresponded exactly with the normal subjects [*41*].

Effect of Prostigmine. Colonic motility is increased by parasympathetic stimulation. Various workers have studied the action of prostigmine or some related agent on the motor activity of the human bowel [*22,54,57*]. There is general agreement that total motility is increased for one half to one and a half hours when a dose of 0.5 to 1 mg. of prostigmine methyl sulphate is administered intramuscularly.

The effect of prostigmine is of interest in relation to the etiology of both the irritable colon syndrome and ulcerative colitis. The irritable colon syndrome has been attributed to enhanced parasympathetic activity by several workers [*58–61*]. In a somewhat similar way, ulcerative colitis has been attributed to parasympathetic overactivity, the resulting muscular spasm or vasodilatation being responsible for the lesions in the colonic mucosa [*27,62–65*].

The comparative effects of prostigmine in these conditions is therefore of interest. Chaudhary and Truelove [*42*] gave 1 mg. prostigmine methyl sulphate intramuscularly to sixteen normal subjects, thirty-five patients with the irritable colon syndrome and thirty-five patients with ulcerative colitis. Normal subjects responded by enhanced colonic motility with a pattern of waves closely similar to that found in patients with spastic colon examined at rest. This in itself supports the thesis that this particular type of colonic dysfunction is related to parasympathetic overactivity, although it might be due to excessive response of the bowel to a normal level of parasympathetic activity. In addition, patients with the irritable colon syndrome characteristically displayed much more colonic activity after a standard dose of prostigmine than did normal subjects. (Fig. 6.) This was true not only for the patients with spastic colon in a stage of symptoms, but also for patients with spastic colon in a symptomless stage when the resting pattern of motility was normal. Likewise, patients who suffered from diarrhoea alone usually showed greater colonic activity than normal subjects after prostigmine administration, although their resting patterns were normal or even hypoactive. These findings suggests that the entire group of patients with the irritable colon syndrome are unduly responsive to parasympathetic stimulation, and that this feature was usually present whether or not they were experiencing symptoms. By contrast, the patients with ulcerative colitis displayed a response to prostigmine which was essentially normal.

Effect of Emotion. Numerous clinical and psychologic observations have suggested that psychologic factors are of importance in the causation of ulcerative colitis [*3,65–71*]. Likewise the importance of psychologic factors in the irritable colon syndrome has been emphasised by many workers [*72–77*]. Nevertheless, very few objective studies have been made of the relationship between emotion and human colonic motility. Weeks [*2*] was able to observe several segments of small and large intestine in an Arab soldier suffering from extensive abdominal wounds. He found that there was a striking increase in the movements of both small and large intestine during a period of "excitement" occasioned by the admission of several other injured Arabs to the ward. Grace, Wolf and Wolff [*3*] studied four male patients with colostomies in whom segments of the large bowel had prolapsed through the original wound. In one subject feelings of depression could be easily induced in the laboratory by talking about specific topics, and these feelings were accompanied by a marked decrease in the motor activity of the right and left sides of the colon. When it was possible to divert him by talking about his "hobby," he became more cheerful and motor activity of the colon increased. Discussion of topics which produced anger, resentment, hostility, anxiety or apprehension resulted in marked hyperaemia and increase in the motility of the colon in all four subjects.

Almy et al. [*6,78–81*] studied the effect of experimentally produced emotional conflicts in intact normal subjects and in patients with the irritable colon syndrome. They induced emotional stress by three methods, namely, immersion of the hand in ice cold water, use of a crown with metal screws around the head, and conflict-producing interviews. In some of the patients the contractile activity of the sigmoid colon was repeatedly observed through a sigmoidoscope, in others contractile activity was recorded by means of a rubber balloon and a water manom-

eter, although they did not specify how many subjects were studied by the one method or the other. Apart from the technical imperfection of their methods for recording motility, experimentally induced pain cannot be regarded as closely similar to the emotional stress experienced by most people at some time in the course of their ordinary lives. For this reason, only the response to interviewing the subjects will be considered. Eight normal subjects were interviewed; four of them showed increased colonic motility during the course of the interview. It was judged that colonic hyperactivity occurred when the subjects regarded the interview as a threat to their own security. Almy et al. also interviewed twenty-nine patients suffering from spastic colon and, in another study, nineteen patients with irritable colon (of whom eight had diarrhoea, seven constipation, and three alternating constipation and diarrhoea). Of the first group of twenty-nine patients, twelve showed an appreciable increase in motility of the sigmoid colon. Of the eighteen patients in the second study, many were said to show an increase in colonic tone with increased frequency and amplitude of colonic contractions, a reaction associated with expressed feelings of hostility and aggression. At some time in the course of the interview, however, all subjects reacted with colonic quiescence, a reaction associated with the replacement of feelings of self-confidence, aggression or hostility by those of hopelessness, inadequacy or self-reproach.

Chaudhary and Truelove [*43*] interviewed eighty-six subjects with simultaneous recordings of colonic motility. The subjects included sixteen normal subjects, thirty-eight patients with irritable colon syndrome and thirty-two patients with ulcerative colitis. A wide range of topics was discussed in which neutral subjects were interspersed with those likely to be emotogenic, such as sexual experiences, marital life, fear of disease and death, careers and other topics thought to be appropriate to the particular subject. In all, twenty-four subjects displayed undoubted colonic hyperactivity in relation to one or more specific topics. However, four of the normal subjects (25 per cent) showed hyperactivity which was little different from the proportions in the two classes of patient; nine patients with ulcerative colitis (28 per cent) and eleven patients with the irritable colon syndrome (29 per cent) showed comparable hyperactivity. In one sense, therefore, this was a negative finding in not showing a striking difference between the patients and the healthy subjects. In another sense, the findings could not be dismissed, because among the patients the topics which caused colonic hyperactivity were those concerned with emotions and events in their lives which appeared to have been of great importance in the genesis or exacerbation of their illness. It was also noticeable that when repeated observations were made on the same patients with ulcerative colitis the maximal responses were obtained when the disease was clinically active. The motor responses of the colon to emotion, therefore, may be of importance in both the irritable colon syndrome and ulcerative colitis, but additional factors must be present to cause the diseases.

RELATIONSHIP BETWEEN MOTILITY OF THE SIGMOID COLON AND THAT OF OTHER PARTS OF THE COLON

Most of the observations on the motility of the human colon have been on the distal colon because this is the only part of the intact organ which is readily accessible for study. However, there are some observations on the motility of other parts of the colon making use of human subjects who possess colostomies. Adler and his group [*21*] studied the proximal descending colon in four subjects with colostomy and it was on the basis of this study that they described the types I, II and III waves which have been dealt with earlier. They found motor activity to be present 41 to 70 per cent of the time of observation. Posey et al. [*24*] recorded the motility of the proximal colon in four subjects with transverse colostomy and compared it with the motility of the sigmoid colon; they found no striking differences. Posey and Bargen [*33*] studied patients with ulcerative colitis and colostomy or ileostomy, but it is not plain whether they found any striking differences between the proximal and distal colon. Grace, Wolf and Wolff made observations on the proximal colon but these were chiefly visual impressions of the behavior of prolapsed segments of bowel and seem to us to be of limited value for this reason. Chaudhary and Truelove [*41*] studied the motility of the proximal transverse colon in two subjects with transverse colostomy and the motility of the upper descending colon in three subjects with leftsided colostomy, and related their findings to the results obtained from the sigmoid colon in healthy subjects with intact colons, the method

of recording being identical. The resting patterns of motility appeared to be closely similar in the colostomy patients and in the healthy control subjects. There was, therefore, a prima facie case for concluding that the motility of the sigmoid colon is a measure of general colonic motility.

Recently, Fink and Friedman [*82*] compared the motility of the distal and proximal colon by introducing polythene tubes from the mouth through the upper gastrointestinal tract as far as the proximal colon while simultaneously registering motility from the distal colon. They concluded that activity of the proximal colon occurs independently of activity of the distal colon and *vice versa*, the point of separation being the mid-transverse colon. Further observations along these lines seem indicated to clarify our knowledge of colonic physiology.

QUANTITATIVE ASPECTS OF COLONIC MOTILITY

It is plainly desirable to be able to express any physiologic function in quantitative terms if scientific progress is to be made. All the earlier workers on colonic motility made use of two parameters. First, they divided the waves into types I, II and III (also type IV in subjects with ulcerative colitis) and recorded their relative frequency. Secondly, they commonly measured the proportion of the total time of observation that the colon displayed motor activity. For example, Spriggs et al. [*28*] studied the motility of the pelvic colon in ten normal subjects and in ten patients with ulcerative colitis. In their normal subjects, type II waves were by far the most common type of activity and motor activity was present for 36.6 per cent of the time of observation. In their patients with ulcerative colitis, type II waves were infrequent compared with normal values whereas the special type IV wave was a prominent feature; motor activity was present for only 19 per cent of the total time of observation.

The most recent workers have been driven to other quantitative approaches to colonic motility because of their inability to classify the waves neatly into types I, II, III and IV. Davidson et al. [*38,39*], although recognising phasic waves and tonus waves, approached the quantitative analysis of their data by dividing waves into different divisions in terms of amplitude and different divisions in terms of duration. From this analysis they concluded that the motor activity of the rectum was different from that of the pelvic colon. They also showed differences between subjects with the diarrhoeal state and those with normal bowel habits.

Chaudhary and Truelove [*41,42*], like Davidson and his co-workers [*38,39*] were not able to classify waves into sharply different types. By analysing their data in terms of amplitude of wave and duration of wave, they were able to show considerable differences between their various clinical categories of subjects. They also made use of a "colonic motility index" as a measure of the total colonic activity of a subject; this likewise showed marked differences between different classes of patients, but the underlying physiologic significance is little understood.

It is apparent that the quantitative assessment of colonic motor function is in its infancy and deserves to be developed.

RELATIONSHIP OF PRESSURE WAVES TO ACTUAL COLONIC MOVEMENTS

Almost all the work on human colonic motility has depended on recording intraluminal pressures either by balloons or open-ended tubes. It is obviously of crucial importance to know what relationship these changes of pressure bears to actual movements of the colon. All the earlier workers interpreted their pressure recordings in terms of colonic movement, but their interpretations were based on indirect evidence and must be regarded with the utmost reserve. Recently Chaudhary and Truelove, in collaboration with their roentgenologist colleague, Dr. G. M. Ardran, made use of cineradiography combined with simultaneous intraluminal pressure recording in seven subjects. Their findings, although of a preliminary nature, permitted the following conclusions: (1) The presence of a wave on the tracing of intraluminal pressures indicated a movement of the colon in the neighbourhood of the recording tip. This was true even for the smallest class of waves dealt with in the study. (2) The bigger the pressure wave, the more pronounced was the colonic movement in the neighbourhood of the recording tip. (3) When big waves occurred, the contents of the colon were projected into a neighbouring section of the bowel.

It was not possible to relate the type of colonic movement to the exact form of the intraluminal pressure wave.

CONCLUDING COMMENTS

The study of human colonic motility is still ill-developed. All the earlier workers employed

balloons, which have both physical and physiologic disadvantages. Their physical properties make them unsatisfactory agents for recording pressures; physiologically, they are likely to stimulate colonic motility, so that an artificial picture is produced. The only two published studies employing modern technics with open-ended tubes coupled to efficient recording systems have yielded results which differ substantially from all earlier work [*38,39,41,42*].

There is a need for studies employing simultaneous cineradiography and pressure recording to elucidate the exact significance of various types of pressure waves in terms of actual colonic movements. Colonic disease and dysfunction are important facets of medicine and will remain poorly understood while our knowledge of colonic physiology, both in health and disease, remains as meagre as it is today.

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Recurrent Polyserositis (Familial Mediterranean Fever; Periodic Disease)*

A Report of Fifty-Five Cases

ERNEST N. EHRENFELD, M.D., MARCEL ELIAKIM, M.D.† *and* MOSHE RACHMILEWITZ, M.D.
Jerusalem, Israel

To the best of our knowledge, the clinical syndrome herein discussed, consisting of recurrent attacks of inflammation of the serous membranes accompanied by fever, was first outlined by Siegal in 1945 [*1*], although single patients previously described were retrospectively suspected to be suffering from the same disorder [*2–6*]. Unaware of Siegal's report, in 1946 two of us (M. R. and E. N. E.) described the first two patients with recurrent polyserositis in Israel as suffering from a new, hitherto unrecognized clinical entity. Since then, close to 100 similar patients have been seen by us, and more have been reported on in the literature [*7–45*]. As the number of diagnosed cases rose, it became apparent that two features are characteristic of the disease, namely, its prevalence in persons of Mediterranean stock, and its frequent familial occurrence [*1,8,10,16–21,24–28,31,40–45*].

Various designations have been used for this syndrome. Siegal originally named it "benign paroxysmal peritonitis" [*1*]. In 1948, Reimann included the syndrome in a group of periodically recurring disorders under the common heading of "periodic disease" [*7*]. This designation has met with many objections, mainly because it lumps together several doubtless unrelated entities [*39,43–46*]. French authors have added names of their own, such as "épanalepsie Méditerranéenne" [*31,39*] or "maladie dite périodique" [*22,30*]. Heller et al. [*44*], impressed by the frequent familial occurrence and the geographic distribution of the disease, suggested the name of "familial Mediterranean fever." Since the cardinal feature of the disease is a recurrent inflammation of the serous membranes, we prefer to call it recurrent polyserositis [*46*].

The purpose of this report is to present our observations on fifty-five patients suffering from recurrent polyserositis who have been observed and studied thoroughly during the past fourteen years. Patients seen occasionally in the Outpatient Department or on consultations are not included in this report.

CLINICAL MATERIAL

Of the fifty-five patients included, thirty-six were male and nineteen were female. The age at onset of overt disease varied between one and forty-seven years, the average being eighteen and one half years. In thirteen patients the disease became apparent before the age of ten years, in sixteen patients between ten and nineteen, in nine patients between twenty and twenty-nine, and in seventeen patients after the age of thirty years. (Table I.) These figures differ slightly from observations reported by others [*1,8–31,44,45*] who found that symptoms appeared before the age of ten in about two thirds of their patients, and before the age of twenty in about 90 per cent. We have four

TABLE I
AGE OF PATIENTS AT ONSET OF THE DISEASE

Age (yr.)	Patients (no.)
1– 9	14
10–19	17
20–29	13
30–39	7
40–49	4

* From the Department of Internal Medicine B, Rothschild Hadassah University Hospital, Jerusalem, Israel.
† Present address: Department of Pharmacology, Schools of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania.

TABLE II
DURATION OF THE DISEASE

Age (yr.)	Patients (no.)
1– 4	11
5– 9	21
10–14	12
15–19	7
20–24	2
25–30	0
31–39	2

patients in whom the disease first appeared after the age of forty. At the time of this study, the disease had lasted from one to thirty-nine years, on the average nine years and one month. (Table II.)

Country of Origin. All the patients were Jews. Most of them hailed from Mediterranean countries; nineteen were born in Israel, sixteen were immigrants from Morocco, nine from Iraq, three each from Tunis and Syria, two each from Russia and Turkey and one from Libya. (Table III.) As to the ethnic origin of the patients, ten were Ashkenazi* (eight Israeli and two Russia-born), while all others were of either Sephardic or Oriental parentage. The presence of Jews of Ashkenazi stock in our series, as well as in others [*40,41,45*], is worth stressing, since it has been claimed that recurrent polyserositis is restricted to Jews of non-Ashkenazi parentage [*44*].

Familial Incidence. The fact that most patients were from large families offered an opportunity to examine the familial incidence of the disease. Our fifty-five patients came from fifty families. Individual members were affected in thirty-five families. More than one case occurred in fifteen families, all of which were non-Ashkenazi (a familial incidence of 30 per cent.) In five of these the disease spread over two generations, while in the remaining ten families only one generation was affected. In seven of the latter ten families, two members were affected; in one, four of eight; in another, five of ten; and in still another, six of eleven siblings had the disease. The familial incidence was established on the basis of the history, as many of the affected relatives were not seen by us.

There were many families with five to ten children of whom only one was affected. However, this fact should be interpreted with caution, since new cases may eventually appear later in life. We have observed families in which the disease first appeared in a second sibling after the age of thirty-two years.

* Ashkenazi Jews are those coming from Europe, America, Australia and South Africa. Orientals hail from various Middle Eastern and North African countries, while Sephardi Jews are those whose ancestors left Spain in the XVth Century and dispersed over various Middle Eastern and European countries.

TABLE III
COUNTRY OF ORIGIN

Country	No. of Cases
Israel	19
Morocco	16
Iraq	9
Tunis	3
Syria	3
Turkey	2
Russia	2
Libya	1
Total	55

Consanguinity between the parents was established in three of the fifteen families in which more than one member was affected; it was denied in eight families, and no data were available in four families.

The presence of amyloidosis was proved in two patients with definitely established familial incidence of the disease. In both of these two families the second sibling was also suspected to suffer from amyloidosis.

SYMPTOMS AND SIGNS (TABLE IV)

Fever during the attacks is one of the most constant and characteristic signs of the disease. It was present in all cases; only occasionally did a few patients have attacks of pain without fever. The temperature usually rose within several hours to 38° or 40°C., although mild attacks were sometimes accompanied by subfebrile temperatures only. Occasionally the rise of temperature was preceded by a chill. The temperature remained elevated for periods varying between several hours and three to four days, although in the majority of cases it became normal within twenty-four hours. Pain in the abdomen and other affected regions usually preceded the appearance of fever by a few hours, and persisted for one or two days after the temperature had returned to normal.

Abdominal pain was present in all patients but one, who exhibited pain in the joints only. As mentioned, the pain preceded the appearance of fever and usually started in the epigastrium or the hypochondrium, or more rarely in other abdominal regions. It spread within a few hours over the whole abdomen, which became tender and distended. On palpation, marked muscular guarding often created the impression of an "acute abdomen." Many patients were there-

fore erroneously exposed to exploratory laparotomy. The pain persisted from one to three days, and subsided gradually thereafter.

Chest pain was present in twenty-one cases. It was usually localized to the lower side of the chest either on the right or on the left, rarely on both sides. The pain caused shallow and rapid respiration, deeper breaths causing much pain. On fluoroscopy, relative immobility and a high position of one or both diaphragmatic leaves was noted during the attacks. Occasionally a transient effusion in the costophrenic sinus could be detected.

Joints were affected in seventeen cases. In one case, attacks of arthritis and fever were the only manifestation of the disease. The large joints, mainly shoulders and knees, were most frequently affected. Swelling, redness and local increase of temperature sometimes accompanied the pain. When the shoulder joints were involved, it was sometimes difficult to establish whether the pain was intrinsically arthritic or referred from the diaphragm. Contrary to other investigators [*39,44*], we have never observed residual damage in the involved joints.

Joint involvement was more frequent in patients with a familial occurrence of the disease. It was observed in ten of the twenty patients with positive family histories, but in only seven of the thirty-five sporadic cases. In three of the four patients with amyloidosis, involvement of the joints was very prominent.

Manifestations in Other Serous Membranes. Besides the peritoneum, pleura and joints, other serous membranes were occasionally affected. Involvement of the pericardium during an attack was suspected clinically in two patients, and diagnosed electrocardiographically in another two. (Fig. 1.) In one case paroxysmal pericarditis accompanied by fever was the only manifestation of the disease for about eighteen months, following which the typical abdominal attacks appeared.

The tunica vaginalis of the testes was affected in two cases, causing testicular pain and tenderness on palpation during an attack. Pronounced headache was experienced by eight patients, but moderate headache was a more frequent symptom. Definite signs of meningeal irritation were never observed.

Other Manifestations. Gastrointestinal symptoms were very frequent. Loss of appetite, nausea and vomiting were complained of in about a fourth of the cases, but when enquired for specifically were found to a minor degree in the majority of the patients. Constipation and meteorism, particularly at the onset of the attack, was a frequent feature, even though seven patients had diarrhea during attacks. Profuse sialorrhea, a symptom described previously [*3,6,29*], preceded the attacks in only one of our patients. Dysuria or polyuria was noted in two patients during attacks. Cutaneous manifestations similar to those already described [*3,8,10,23,39,44*] were seen in only four cases. They appeared on different occasions as either purpura or erythema, and sometimes as periarticular subcutaneous nodules.

Only three patients had manifestations of allergic nature; bronchial asthma in two and vasomotor rhinitis in one. This low incidence is worth stressing, in view of the frequent finding by Siegal and Reimann [*9,12*] of allergic phenomena in either the patients or their relatives.

TABLE IV
SYMPTOMS AND SIGNS IN FIFTY-FIVE PATIENTS WITH RECURRENT POLYSEROSITIS

Symptoms and Signs	Patients	
	No.	Per cent
Main symptoms		
Abdominal pain	54	98
Fever	55	100
Pleuritic pain	21	38
Joint pain* (sometimes accompanied by swelling)	17	31
Minor or less frequent symptoms		
Constipation	28	51
Vomiting	20	36
Severe headache	8	15
Diarrhea	7	13
Skin rash	4	7
Pericardial pain	2	4
Disturbance in micturition	2	4
Pain in testes	2	4
Sialorrhea	1	2
Physical signs in the attack-free intervals		
Palpable spleen	22	40
Colloid body-like dots in the eye grounds (of forty-two examined)		
Numerous	11	26
Few	10	24
Systolic murmur over apex and parasternal	16	29
Palpable (probably enlarged) liver	15	27

* One patient had arthritis only.

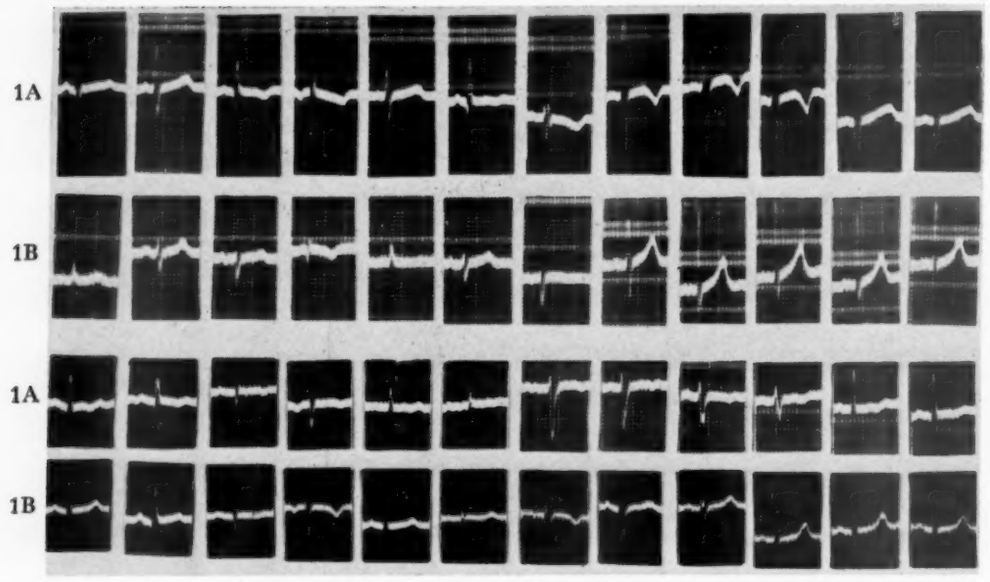


FIG. 1. Electrocardiographic changes in attack (A) and in the interval between attacks (B) in two patients with recurrent polyserositis. Note indications of pericarditis on the day of attack in the upper tracing. The second case (lower tracing) showed non-specific changes in the T wave during the attack. From: ELIALIM, M. and EHRENFELD, E. N. *Am. J. Cardiol.*, 7: 517, 1961 [*52*].

Of the ten married women in our series who were in the child-bearing age while suffering from the disease, four were sterile. In two of these women tubal obliteration was found, and probably constituted the cause for sterility. Four other women had a total of nine children, and in two women no information as to parity was available.

Psychiatric Aspects. Many patients showed neurotic trends, probably caused by the impact of the chronically recurrent attacks on their personality. Disruption of families and conflicts at the place of work occurred not infrequently as a result of the disease. Some patients, in despair, travelled from one medical center to another, sometimes from one continent to another, in search of a remedy. Patients afflicted with amyloidosis and those with a familial incidence were particularly liable to depressive reactions.

On the other hand, some patients tried to minimize the importance of the disease and continued to work even during the days of attacks, usually with the help of analgesic drugs.

A typical attack usually starts with discomfort in the epigastric, hypochondric or periumbilical region, building up gradually to severe pain. As the temperature starts to rise, the pain spreads within a few hours all over the abdomen. The abdomen becomes tender and extremely sensitive to the lightest touch. On examination at this stage no peristalsis is usually perceptible, and rebound tenderness is pronounced. The pain is sometimes localized to a restricted abdominal area, thus giving the erroneous impression of localized visceral disease with secondary peritoneal involvement. Many of the cases were misdiagnosed in the early stages of the disease as gallbladder disease, amebic hepatitis, appendicitis or perforated ulcer. Sometimes, apparently when the posterior aspect of the peritoneum is affected, the pain is localized to the lumbar regions, and the condition is misdiagnosed as acute renal colic. After a variable period of twelve hours to several days, the temperature falls more or less abruptly, while the pain subsides more gradually, persisting for one to three days. In the intervals between attacks most of the patients are entirely symptom-free, a fact of great importance in the differential diagnosis.

Periodicity. Although the designation of "periodic disease," implying a regular recurrence of attacks, has been widely employed for this disorder, in our series, as well as in others, the intervals between attacks varied considerably, even in the same patient. The shortest interval in our series was two days, one attack overlapping with the next. This, however, was an unusual occurrence. More frequently the intervals varied between several days and several weeks. In some patients, spontaneous remissions for as

long as three years occurred, and one of our patients (a young woman aged thirty) has now been symptom-free for five years. The remissions appeared sometimes during pregnancy, after laparotomy and after changes in environment, such as climate or enlistment in the army. Many patients volunteered the statement that cold weather had a detrimental effect; it would precipitate attacks in patients in remission, and shorten the intervals between attacks in patients who had infrequent attacks. On the other hand, in some patients a remarkable regularity in the appearance of the attacks was noted. The most common regular interval was seven days. Some patients whose attacks appeared regularly at one stage of the disease, exhibited (without any obvious reason) long and irregular intervals at another.

Environmental Influences. Besides cold, no other precipitating cause could definitely be ascertained. Some patients claimed that emotional strain precipitated the attacks, whilst others were convinced of the opposite. Physical exertion appeared rather to precipitate attacks. In seven patients the onset of the disease was within one year after immigration to Israel. Some patients thought that the physical and mental strain related to adaptation to a new environment was the cause of their disease.

Pregnancy suppressed the attacks in at least two patients, in one of them repeatedly. In two patients the attacks tended to appear with menstruation. A similar patient, described by Sison et al. [*47*], was suspected to be sensitive to endogenous estrogen. In one of our patients tubal insufflation for investigation of sterility caused a violent exacerbation of the disease lasting ten days, and thereafter a remission which has so far lasted five years.

PHYSICAL EXAMINATION IN THE ATTACK-FREE INTERVALS (TABLE IV)

In the interval between attacks, physical signs were meager, and frequently altogether absent. The habitus of the patient was usually asthenic.

Changes in the eye grounds were found in 50 per cent of the cases. As previously described [*48,49*], the changes consisted of dotted, porcelain white or yellowish lesions, 70 to 300 μ in size, and localized in Bruch's membrane. In most cases the dots had a punched-out appearance, rarely with a pigmented margin. A peculiar, quasi-geometric distribution of the dots, suggestive of domino, was quite frequent. (Fig. 2.) In many cases the lesions were indistinguishable from colloid bodies seen in the aged, and may easily have been overlooked in other reported cases. However, the lesions described herein were found in twenty-one of the forty-two patients examined. The average age of the patients with positive fundal findings was thirty-two years, including several children. In eleven cases the dots were numerous and widespread in both fundi, while in the remaining ten cases there were few or isolated dots. In a control series of 232 apparently healthy subjects, numerous dots without other fundal changes were found in 4 per cent, and few dots in an additional 7 per cent. The average age of the patients from the control group with "positive" findings was higher (forty years) than that of the respective group of patients with recurrent polyserositis.

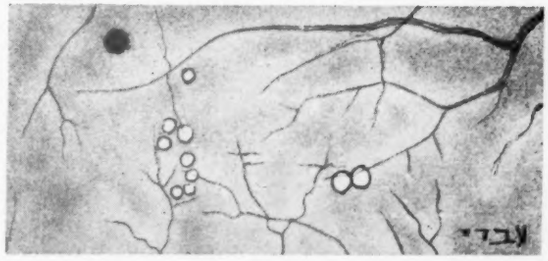


FIG. 2. Colloid body-like dots in the fundus of a patient with recurrent polyserositis. From: MICHAELSON, I., ELIAKIM, M., EHRENFELD, E. N. and RACHMILEWITZ, M. *Arch. Ophth.*, 62: 1, 1959 [*49*].

The duration of the disease and the familial incidence were not related to the presence of the fundal changes. Only one of four patients with proved amyloidosis had the fundal lesion.

Enlargement of Liver and Spleen. The spleen was felt in twenty-two patients (40 per cent). All four patients with proved amyloidosis had a palpable spleen. Usually only the tip was palpable, and marked enlargement was rare. The spleen was firm and not tender. In one case it was removed, in another hospital, and the histologic examination revealed only chronic congestion. Splenectomy did not affect the course of the disease in this patient.

Some enlargement of the liver was found in fifteen patients, amongst them two with proved amyloidosis. Liver biopsies performed in two of our patients without amyloidosis failed to reveal any abnormal findings. This observation is contrary to the finding of Brick and Cajigas

[*13*] of fatty changes in the liver in a patient with this disorder; it is doubtful whether these changes were at all related to the basic disease.

Cardiac Manifestations. A pericardial friction rub was never heard, although, as previously mentioned, other clinical or electrocardiographic evidence of pericarditis was found in four cases. Systolic murmurs over the apex and Erb's point were present in sixteen cases. The murmur was always soft and blowing in character, and did not exceed grade 2. In five patients the murmur was indistinguishable from that found in rheumatic mitral valvular disease. In two patients aortic systolic murmurs were heard as well. The second pulmonary sound was accentuated in six instances. Rheumatic mitral valvular disease was suspected in four patients, combined mitral and aortic valvulitis in one patient, and aortic stenosis in one. In two patients clinically suspected of rheumatic valvular disease, amyloidosis of the heart was found at autopsy.

Findings at Laparotomy. Since the disease frequently manifests itself as an "acute abdomen," many patients are subjected to surgical exploration. In the present series fifteen patients were operated upon, three of them on two occasions each. The presumptive diagnosis was acute appendicitis in eleven instances, acute cholecystitis in two, and perforated ulcer in another two. These diagnoses were not confirmed at surgical intervention. Many more patients escaped operation as they were well aware of the transitory nature of the attacks, and so warned the surgeons. Exploratory laparotomy is so frequently performed on patients with recurrent polyserositis as to constitute a characteristic anamnestic detail of the disease.

On laparotomy the only abnormal findings were edema of the peritoneum and enlarged lymph nodes. Histologic examination of the peritoneum revealed infiltration, frequently around distended capillaries, with neutrophils, round cells and sometimes eosinophils. Proliferation of adventitial cells was also found. A small quantity of free exudate was occasionally seen in the peritoneal cavity. It is to be noted that no adhesions were ever found, unless the patient had been operated upon before. Two of our patients who had undergone appendectomy had to be reoperated on because of ileus caused by fibrous bands produced by the previous surgical intervention. Examination of the lymph glands revealed non-specific inflammatory changes.

LABORATORY EXAMINATIONS

Urine. Proteinuria was present on repeated occasions in six of fifty-five patients. In four of these the diagnosis of amyloidosis was established by renal biopsy or at autopsy. In the remaining two there was no other evidence of amyloidosis, and results of the Congo red test were negative. Microscopic hematuria was occasionally found in the patients with amyloidosis. No other abnormal urinary findings were present in any of the patients. Porphobilinogen was repeatedly looked for in fifteen patients during attacks and in the attack-free intervals, but was never found.

Stool. Repeated stool examinations for ova, parasites and pathogenic flora were performed in all patients. Two patients had lambliasis, two had amebiasis, and in one ova of ascaris were found. These findings are to be expected in a comparable control hospital population. All cultures for shigella and salmonella organisms were negative.

Hematologic Findings. The leukocyte count was usually between 12,000 and 18,000 per cu. mm. during an attack, with a normal differential count. However, three patients had leukopenia, as low as 3,000 per cu. mm. during the attacks. The change in the white blood count occurred within several hours of the onset of the attack and was transient, lasting about one day as a rule.

Several authors have reported finding of evidence of increased hemolysis in patients with recurrent polyserositis. Benhamou et al. found a positive reaction to the direct or indirect Coombs' tests in some of their patients [*32,35*], a finding not confirmed by other investigators [*39,44*]. De Vries et al. [*40*] found spherocytes in all of their patients with recurrent polyserositis, both during attacks and in the free intervals. The latter investigators observed, by means of the electron microscope, abnormalities in the structure of the red cells and discovered, in the serum of seven patients, an antibody which agglutinated normal papainized red cells O. Other investigators have failed to demonstrate circulating antibodies in patients with this disorder [*1,8,39,44*].

Despite the evidence of increased blood destruction in recurrent polyserositis, anemia is the exception rather than the rule. In the large majority of our patients there were no changes in the red cell count, although a few had a mild

hypochromic or normochromic anemia. In these cases the level of hemoglobin was never less than 9 gm. per cent. Although similar levels of hemoglobin are frequent in our hospital population, it is assumed that at least in some cases the anemia was related to the disease, since a rapid fall in the level of hemoglobin was observed during a short period of numerous recurrent attacks. The red cell life span was examined in two patients during a period of frequent attacks, and found to be shortened in both (fifteen and nineteen days, respectively, instead of twenty-six to thirty days, using the Cr^{51} method). Osmotic fragility of the red blood cells was normal in three cases and increased in one. Spherocytes were not conspicuous on routine blood examinations. The reaction to the Coombs' tests, both direct and indirect, was negative in eight patients examined. The bone marrow was examined in four patients and found to be normal.

In view of these findings the impression is gained that increased hemolysis, when present, is a secondary manifestation of the disease.

Bacteriologic and Serologic Examinations. Numerous cultures of urine, stool and sputum (for Mycobacterium tuberculosis) were negative. Repeated blood cultures taken in twenty patients during attacks remained sterile. Throat swabs examined in seventeen patients grew out hemolytic streptococci in two, and no pathogenic bacteria in the remaining fifteen. Thick drop preparations were taken from more than half of the patients, and were always negative for malaria parasites and Borrelia recurrentis. Results of Wassermann and Kahn tests were negative in all patients. Results of agglutination tests were negative for enteric fever in twenty-five patients, and for brucellosis in twenty-two patients. The reaction to the Paul-Bunnell test was negative in fourteen cases. Antistreptolysin-O titers were normal in seven cases and elevated in six (200 to 1,500 units per ml.). C-reactive protein was normal in the intervals between attacks in five cases, and abnormal on, or close to the day of, attack in nine cases. Cold agglutinins were looked for in eight cases and found in none. Blood complement was normal in all five patients examined. No L.E. cells were found in seven patients in whom they were looked for. The Weinberg reaction was negative in six patients. The Rose-Waaler test was negative in four patients with joint complaints. Results of skin tests for brucellosis, echinococcosis, schistosomiasis and sarcoidosis were negative in eight cases.

TABLE V
HYPERSENSITIVITY TO OLD TUBERCULIN IN EIGHT PATIENTS WITH RECURRENT POLYSEROSITIS

Case	Maximal Dilution Causing Skin Reaction	Paroxysms Provoked
1	1:100,000,000	No
2	1:10,000,000	Yes
3	1:10,000,000	Yes
4	1:10,000,000	Yes
5	1:1,000,000	Yes
6	1:1,000,000	No (?)
7	1:1,000,000	No
8	1:100,000*	Yes

* Following treatment with ACTH, 1:100,000,000 tuberculin repeatedly induced typical paroxysms, although the skin reaction was negative.

Sensitivity to Tuberculin. In the course of routine examination of these patients we were impressed by the fact that some of them showed striking sensitivity to tuberculin. The intradermal injection of minute quantities of tuberculin provoked not only a local reaction but frequently also paroxysms indistinguishable from the spontaneous attacks.

Forty-three of our patients were tested with old tuberculin (O.T.) using 0.1 ml. of dilutions from 1:1,000 to 1:100,000,000. Most patients were initially tested with 1:10,000; if the reaction was positive, they were further tested with increasing dilutions until a weak positive or a negative result was obtained. Those who did not react were tested with higher concentrations up to 1:1,000, and if no reaction was noted the patient was considered negative. A positive reaction to a dilution up to 1:100,000 was considered a normal response. Patients who reacted to dilutions above 1:100,000 were considered hypersensitive.

Twenty-three of the patients showed no reaction to O.T., and twelve showed a normal response. Three of the latter exhibited minor general reactions after the administration of O.T. in a dilution up to 1:10,000; two had an abortive slight rise of temperature, and one had abdominal pain without fever. In eight patients, positive reactions were observed with dilutions ranging from 1:1,000,000 to 1:100,000,000. In five of these, attacks followed within twenty-four to forty-eight hours of the administration of the minute amount of O.T. (Table v.) In one pa-

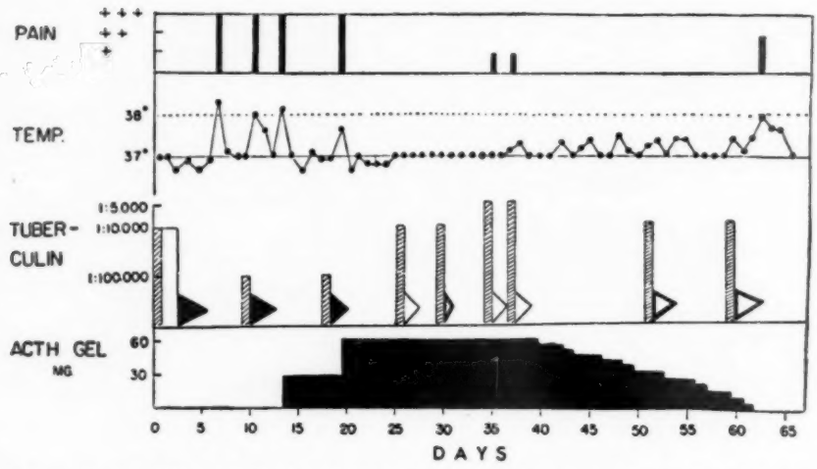


FIG. 3. Provocation of attacks of polyserositis by old tuberculin and their suppression by ACTH. Skin reactions: black triangle indicates marked reaction; triangle with wide edges, mild reaction; and triangle with thin edges, doubtful reaction. Bar before triangle indicates dilution of tuberculin used. From: RACHMILEWITZ, M., EHRENFELD, E. N. and ELIAKIM, M. C. *Israel M. J.*, 17: 150, 1958 [*43*].

tient ACTH suppressed both the local and the general reaction to tuberculin. (Fig. 3.) In the same patient, following withdrawal of ACTH, it was possible to provoke a general reaction with minute quantities of O.T., in the absence of any local reaction.

Erythrocyte Sedimentation Rate. All patients exhibited an increase in the erythrocyte sedimentation rate on the day of attack or shortly thereafter. The values were usually higher than 30 mm. after one hour (Westergren), and occasionally as high as 120 mm. If the intervals between the attacks were long enough, the values tended to return to normal, although in many cases they remained elevated. The patients with amyloidosis had still higher values which reached 145 mm. per hour after an attack in one case. In all of these patients the erythrocyte sedimentation rate remained markedly increased during the attack-free intervals.

Blood Chemical Findings. Routine urea and glucose determinations were within normal limits in all patients, except for the high values of blood urea in some of the patients with amyloidosis. Liver function tests were performed in thirty-one patients, and occasional deviations were observed in four. Serum uric acid levels were normal in seven patients with joint complaints.

Electrophoresis of the serum proteins was performed in ten patients on the day of attack, and in sixteen patients during the intervals between attacks. The values of the determinations performed on the day of attack (excluding the patients with amyloidosis) showed marked variations from one patient to another but on the average, were only slightly different from the average control values. (Table VI.) The main deviations from the control values were a decrease of the serum albumin fraction, a slight increase in α_2, and the appearance (in two cases) of an abnormal peak in the β fraction (0.54 and 0.58 gm. per cent, respectively); in both cases the abnormal peak was absent during the attack-free intervals. In the intervals between attacks the average serum albumin level was slightly higher than on the day of attack, but it was still lower than normal; the α_2 fraction was normal.

Electrophoresis of the serum proteins in three patients with proved amyloidosis and nephrotic syndrome showed a marked reduction of albumin and γ globulin, and a rise in α_2. No abnormal peaks, such as were observed by Block et al. [*50,51*] in patients with primary amyloidosis, were found in our patients although, as already mentioned, abnormal β globulins were present during attacks in two patients without evidence of amyloidosis.

Fibrinogen was increased in the plasma of five patients during the attacks (540 to 750 mg. per cent), and normal in three of them in the intervals between attacks.

Electrocardiographic Findings. Electrocardiograms were available in thirty-one patients. In

TABLE VI

ELECTROPHORESIS OF SERUM PROTEINS IN PATIENTS WITH RECURRENT POLYSEROSITIS

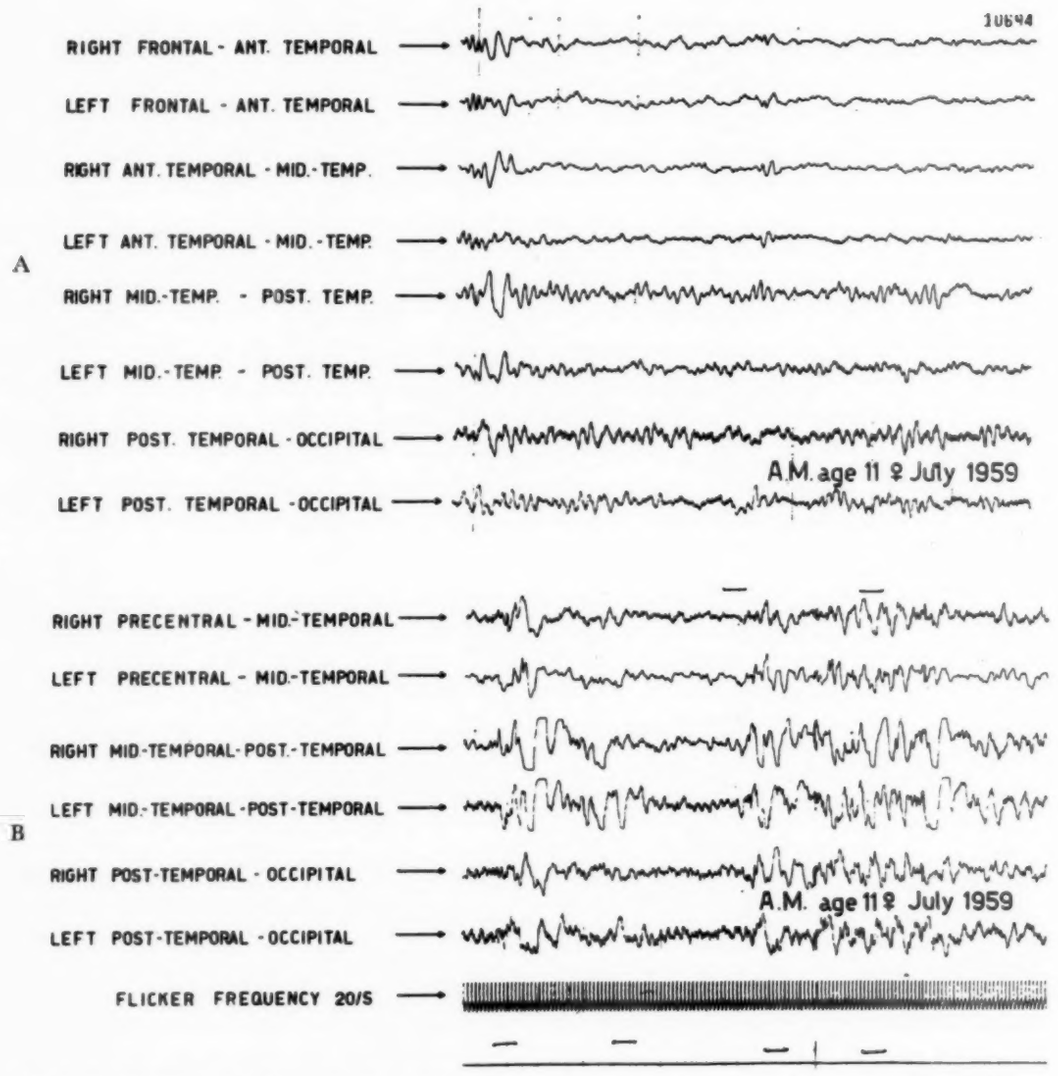
	Patients (no.)	Total Protein (gm.%)	Albumin (gm.%)	Globulin (gm. %)				
				α_1	α_2	β	γ	"X"*
Patients without Amyloidosis								
Day of attack	10	6.95 (6.5–7.6)	2.92 (2.0–4.3)	0.34 (0.24–0.48)	1.08 (0.92–1.44)	1.16 (0.53–1.53)	1.29 (0.51–1.97)	0.54 0.58
Interval	13	7.0 (5.9–7.8)	3.04 (2.10–4.35)	0.45 (0.20–0.93)	0.89 (0.52–1.32)	1.13 (0.27–1.66)	1.49 (0.61–2.18)	
Patients with Amyloidosis								
L. H. (3/13/56)		6.2	1.54	0.34	1.32	1.42	1.58	
(8/2/56)†		6.0	1.41	0.78	1.71	1.20	0.90	
K. M.		4.8	1.00	0.44	1.55	1.10	0.71	
S. I.		2.9	0.72	0.12	0.81	0.67	0.58	
Normal Subjects								
		7.4 (7.0–7.7)	3.62 (3.4–3.8)	0.45 (0.30–0.55)	0.89 (0.6–1.1)	1.04 (0.80–1.15)	1.40 (1.10–1.55)	

* Found only during attack in two patients, between the β_1 and β_2 fractions.
† Died 12/31/56.

thirteen of them the electrocardiogram was obtained during an attack, and in twenty-five records were taken in the intervals between attacks. Electrocardiographic abnormalities were found in four patients examined during attacks [*52*]. In two of these the changes were suggestive of pericarditis; in the remaining two they were not specific and were confined to the T wave. (Fig. 1.) In three of these four patients normal tracings were recorded during the interval between attacks, while in the fourth a normal electrocardiogram was recorded during another attack. In none of the patients examined between attacks were abnormalities present in the electrocardiogram.

Electroencephalographic Findings. Electroencephalograms were recorded in sixteen patients. A total of twenty-seven records were taken, twelve during attacks and fifteen in the intervals between attacks. In four of the ten patients examined during attacks the records were abnormal [*53*]. In two of them the records were normal after the attacks, in one patient the record remained abnormal and in one patient no re-examination was performed. Of six patients examined only during the intervals between attacks, abnormal records were found in three. The main feature of the electroencephalographic abnormality was a generalized irregular activity and non-specific diffuse theta activity of 5 to 6 c.p.s. Occasionally, sharp waves were recorded in some of the cases. In two cases slow, sharp and even spiky waves, suggesting an epileptic trend, were recorded, especially after hyperventilation and photic stimulation. (Fig. 4.) Analysis of the patients with abnormal electroencephalographic records revealed that these were patients with a high frequency of attacks or long duration of the disease. Visceral manifestations were more frequent in these patients [*53*].

X-ray Findings. Numerous x-ray studies were made in most of the patients. These included roentgenograms of the chest, gastrointestinal tract, urinary passages, and gallbladder studies. The only abnormality observed repeatedly was a high, almost immobile diaphragm; in the great majority of cases the right leaf was affected, and its elevation was sometimes accompanied by a small effusion in the costophrenic sinus during the attack. This effusion, as well as the immobility of the diaphragm, were of short duration, and normal conditions were often found as soon as


RIGHT FRONTAL - ANT. TEMPORAL
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A
RIGHT MID.-TEMP. - POST. TEMP.
LEFT MID.-TEMP. - POST. TEMP.
RIGHT POST. TEMPORAL - OCCIPITAL
A.M. age 11 ♀ July 1959
LEFT POST. TEMPORAL - OCCIPITAL
RIGHT PRECENTRAL - MID.-TEMPORAL
LEFT PRECENTRAL - MID.-TEMPORAL
RIGHT MID-TEMPORAL - POST.-TEMPORAL
LEFT MID.-TEMPORAL - POST-TEMPORAL
B
RIGHT POST-TEMPORAL - OCCIPITAL
A.M. age 11 ♀ July 1959
LEFT POST-TEMPORAL - OCCIPITAL
FLICKER FREQUENCY 20/S

FIG. 4. Electroencephalograms of a patient with recurrent polyserositis. A, at rest. Note diffuse irregular theta activity with occasional sharp waves. B, during flicker stimulation. Note bursts of slow high waves and occasional spikes. From: ELIAKIM, M. and BENTAL, E. *Arch. Int. Med.* [*53*].

twenty-four hours after an attack. These changes were present in almost all the twenty-three patients in whom the chest was fluoroscoped during an attack. In five patients who had apical systolic murmurs and accentuated second pulmonary sounds, the x-ray silhouette of the heart showed slight prominence of the pulmonary segment. No other findings relevant to the disease were encountered. Incidental findings such as chronic duodenal ulcer or nephrolithiasis were present in very few patients.

RECURRENT POLYSEROSITIS AND AMYLOIDOSIS

The occurrence of amyloidosis in patients with recurrent polyserositis is well established. The first clinical description of the renal complications of amyloidosis in this disorder was given by Mamou and Cattan [*16*]. Later, Mamou reported the anatomic-pathologic changes in one case of recurrent polyserositis with generalized amyloidosis [*54*]. Additional reports appeared thereafter [*39,44,55*].

In our series, amyloidosis was proved by either renal biopsy or autopsy in four cases. Two additional patients had albuminuria, but results of their Congo red tests were negative and no other evidence of amyloidosis was present. Another patient had a strongly positive reaction to the Congo red test but no albuminuria; a gingival biopsy failed to reveal amyloid deposits.

TABLE VII

SUMMARY OF MAIN DATA IN PATIENTS WITH RECURRENT POLYSEROSITIS AND AMYLOIDOSIS

Patient	Familial Incidence	Course of Disease	Colloid-like Bodies in Eye Grounds	Enlarged Spleen	Enlarged Liver	Nephrotic Syndrome	Heart Findings	Maximal Erythrocyte Sedimentation Rate (mm./hr.)	Maximal White Blood Cells (cu. mm.)	Congo Red Test	Pathological Findings
L. H.	Brother, recurrent polyserositis (suspected amyloidosis); mother, "rheumatism"	Age 2, polyarthritis with fever; later paroxysmal Age 10, heart murmurs Age 16, paroxysmal peritonitis; hepatosplenomegaly; nephrotic syndrome Age 18, death; renal failure	−	+	+	+	+	107	33,000	+	Amyloidosis of kidneys, skin, myocardium, endocardium, vessels of spleen, liver, ovary, adrenals
K. M.	Brother, "rheumatism"	Age 15, polyarthritis with fever Age 17, paroxysmal joint, chest pain and fever; splenomegaly; heart murmur Age 19, paroxysmal peritonitis; traces of albumin in urine Age 14, death; renal failure	−	+	+	+	+	145	39,000	+	Amyloidosis of kidneys, spleen, heart and adrenals
S. I.	Five brothers died during childhood	Age 26, polyarthritis with fever lasting several months Age 28, paroxysmal peritonitis Age 29, albuminuria; splenomegaly; fate unknown	+	+ −	−	+	−	120	22,000	+	Amyloidosis of kidneys (biopsy)
T. N.	One sister, recurrent polyserositis; suspected amyloidosis	Age 26, paroxysmal pleuritis; later also peritonitis Age 28, only paroxysmal peritonitis albuminuria Age 30, nephrotic syndrome	−	+	+	+	−	?	?	?	Amyloidosis of kidneys (biopsy)

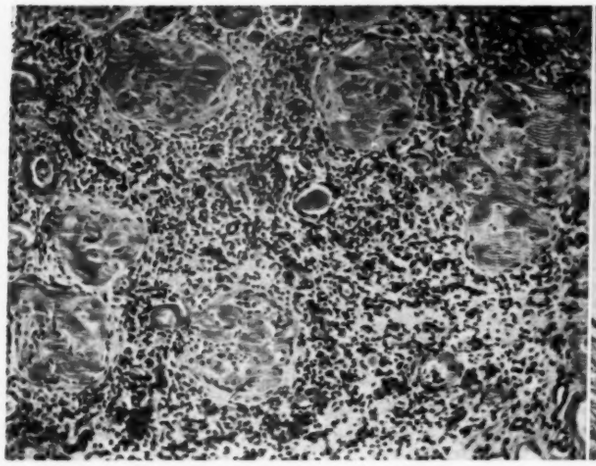

FIG. 5

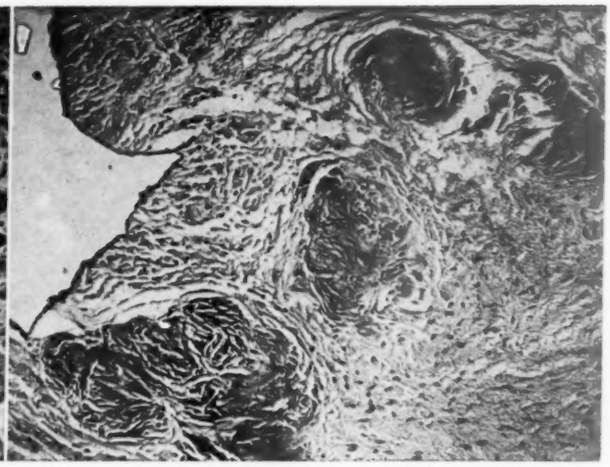

FIG. 6

FIG. 5. Kidney of a patient with recurrent polyserositis and amyloidosis. Hematoxylin and eosin stain, orignal magnification × 120. The glomeruli are almost entirely replaced by amyloid. Note also amyloidosis of afferent arterioles. Slight interstitial infiltration is present.

FIG. 6. Endocardium of a patient with recurrent polyserositis. Hematoxylin and eosin stain, original magnification × 120. Heavy amyloid deposits are seen beneath the mitral leaflets. Similar nodular deposits were widespread in the leaflets themselves.

In still another patient, amyloidosis was suspected because the clinical course was very similar to that of his sister who died in our hospital of amyloidosis (L. H., Table VII). However, he had no albuminuria and the reaction to the Congo red test was negative.

It may be seen from Table VII that in two of the cases of recurrent polyserositis with amyloidosis the disease was familial. The affected relatives were strongly suspected of suffering from amyloidosis as well. The remaining two patients were also suspected of having relatives suffering from recurrent polyserositis, although this could not be proved. It is remarkable that in almost all the cases of amyloidosis reported the patients belonged to families in which other members were also affected by both recurrent polyserositis and amyloidosis.

The clinical course in patients with amyloidosis seemed to follow a distinct pattern. In three of the four patients the initial manifestation of the disease was arthritis accompanied by fever which was misdiagnosed as rheumatic fever. The antistreptolysin-O titer was not elevated in these cases. Later on, arthritis became paroxysmal and attacks of abdominal and chest pain appeared as well. Hepatosplenomegaly was a prominent clinical finding, and heart murmurs simulating rheumatic heart disease also were present. Eventually, albuminuria appeared and the renal lesion progressed rapidly to the full blown nephrotic syndrome and renal insufficiency. At this stage, the leukocyte count was persistently high and the erythrocyte sedimentation rate was excessive. In two patients who came to autopsy, amyloidosis of the kidneys, heart, muscles, adrenal, ovaries, spleen, skin and intestines was found. (Figs. 5 and 6.) In two patients in whom rheumatic valvular disease had been suspected clinically, amyloidosis of the valvular leaflets was found at autopsy. (Fig. 6.)

DIFFERENTIAL DIAGNOSIS

Besides the surgical conditions already mentioned, other differential diagnostic possibilities have to be considered, especially in the early phase of the disease, before its recurrent nature becomes apparent. Of the various diagnoses considered, gallbladder disease, amebic hepatitis and acute peptic ulcer were the most frequent, since the pain very often started in the epigastrium or the right hypochondrium. Other diagnoses suspected in some cases were porphyria and the abdominal equivalents of epilepsy. Porphyria could be excluded by the absence of porphobilinogen in the urine. Abdominal epilepsy occasionally presented a more difficult diagnosis to reject because of the evidence of electroencephalographic changes of the convulsive type. The correct diagnosis could be established in view of the presence of clinical

and laboratory signs of an acute inflammatory process, muscular rigidity, the long duration of the attack and lack of effect of anticonvulsive drugs.

TREATMENT

As some of our patients were treated as early as 1942, the whole gamut of sulpha drugs and antibiotics, as they became available, was tried. Although it is difficult to evaluate any drug action on a disease as capricious as recurrent polyserositis, it became apparent that none of these drugs had any effect on the course of the disease. Other chemotherapeutica, such as antihistamines, chloroquin, para-aminobenzoic acid, triethylene melamine and nitrogen mustard, were tried out, with the same disappointing results. When ACTH and corticosteroids became available, they were tested in fifteen patients. There is no doubt that in eleven patients suppression of attacks, or at least prolongation of the intervals between them, was achieved with large doses of these drugs (more than 50 units of ACTH gel or more than 20 mg. of prednisone daily). These drugs obviously could not be given indefinitely in such dosage, in view of the side effects and failure to achieve complete remission. Severe rebound reactions were sometimes observed, even after gradual discontinuation of the steroids. More recently, two young girls have been treated with phenylbutazone, 200 mg. daily, apparently with a beneficial result; however, it is too early to evaluate this fully.

Desensitization with tuberculin was attempted in six patients hypersensitive to O.T., but only two patients were sufficiently cooperative to continue the treatment for several months. In these two patients the skin sensitivity decreased and clinical remissions of about eighteen months were achieved. In one of these two patients a second attempt at desensitization, following recurrence of the attacks, failed to bring about relief of symptoms, although the skin sensitivity diminished markedly.

PROGNOSIS

In the majority of cases recurrent polyserositis runs a benign course. We have been impressed, as have been most authors dealing with this disease, with the perfect state of health of most patients in the intervals between attacks, despite the long duration of the disease. One of our patients has had more than a thousand attacks of peritonitis in the course of thirty-nine years and is nevertheless in perfect general condition. This patient is the oldest in our series, now sixty-two years of age; three other patients have reached the age of fifty years or more. The longest full remission (still continuing) has been five years. We would hesitate to call this patient cured, since the course of the disease is so unpredictable, and attacks may still recur, as they have after remissions lasting as long as three years.

As mentioned previously, amyloidosis developed in four (7.2 per cent) of our patients. When amyloidosis affects the kidneys, a rapid downhill course ensues, resulting in a fatal outcome within a short period of time. Two of our patients with amyloidosis succumbed to the disease, while the other two escaped our observation.

Our two patients with albuminuria, which has persisted for a number of years, are in good general condition. Although amyloidosis has not been ruled out in these two patients, it is quite possible that the albuminuria is due to another cause. Glomerulonephritis has been described as a complication of recurrent polyserositis [*39*], and in any event albuminuria does not necessarily signify amyloidosis of the kidneys.

THE NATURE OF THE DISEASE

The nature of recurrent polyserositis is still in the realm of speculation. The possibility of a bacterial or viral etiology is extremely remote, in view of the familial occurrence, the finding of the disorder only in certain ethnic groups, the clinical course, the negative results of all bacteriologic and serologic investigations and, finally, failure of antibiotics and other antibacterial agents to affect the course of the disease.

The paroxysmal occurrence of the attacks in recurrent polyserositis has led to a comparison between this disease and epilepsy [*1,12*]. The occasional presence of fever in the abdominal equivalent of epilepsy [*56,57*], as well as the finding of electroencephalographic changes, sometimes of the convulsive type in recurrent polyserositis [*53*], are in keeping with this idea. Furthermore, both epilepsy and recurrent polyserositis tend to be familial. However, the finding of acute inflammatory changes in the serous membranes, a fundamental feature of recurrent polyserositis is incompatible with the diagnosis of epilepsy. Likewise, anticonvulsive treatment is of no avail in this disorder.

The frequent familial incidence and the occurrence of the syndrome apparently only in people living in or hailing from a limited geographical area, has suggested the possibility that a hereditary inborn error of metabolism may be operative [*44*]. So far there is no objective evidence to support this hypothesis. However, two recent observations may be of interest in this connection. Bondy et al. reported that two patients with recurrent polyserositis excreted abnormally large amounts of pyrogenic adrenal androgen, ethiocholanolone, in the urine during the attacks [*58*]. De Vries et al. described an abnormality in the red cell membrane detected by the electronmicroscope, and an antibody against normal papainized red cells O in patients with recurrent polyserositis, as well as in their unaffected relatives [*40*]. Neither of these findings has so far been confirmed by other investigators.

A parallelism has been drawn between recurrent polyserositis and the collagen diseases [*55*]. The clinical resemblance of some cases of recurrent polyserositis to rheumatic fever, lupus erythematodes disseminatus or polyarteritis nodosa has been used as an argument in favor of this theory. However, results of the L.E. test are consistently negative in recurrent polyserositis; biopsies have rarely revealed polyarteritis; and "hematoxylin bodies" and fibrinoid degeneration, the fundamental lesions in the collagen diseases, have never been found in recurrent polyserositis.

There is some evidence to favor an allergic basis for recurrent polyserositis. The paroxysmal and intermittent nature of the attacks resembles other allergic diseases, e.g., bronchial asthma, urticaria and angioneurotic edema. The basic morphologic alteration during the attack is an acute dilatation of small vessels, with exudation sometimes rich in eosinophils. Similar changes are characteristic of most allergic conditions. The onset of the disease early in life, usually without permanent impairment of health, is also consistent with the allergic concept of the disease. The familial incidence is suggestive of a genetic factor, which is usually present in allergic disorders of the humoral type, e.g., atopic dermatitis. The therapeutic effect of ACTH and corticosteroids also is in keeping with an allergic etiology.

The main objection to the allergic concept of recurrent polyserositis is the failure in most cases to identify the noxious allergen. In only a few cases could food allergens [*5,6,39*] or endogenous estrogen [*47*] be incriminated as the cause of the disease. The demonstration of hypersensitivity to tuberculin in a limited group of patients with recurrent polyserositis is of special interest in this respect. Although the exact relationship between the hypersensitivity to tuberculin and the disease has not been elucidated, this finding cannot be dismissed as incidental. In the hypersensitive patients, typical attacks could be repeatedly provoked by the injection of minute quantities of tuberculin, and clinical remissions could be achieved in some cases by means of desensitization with old tuberculin. Other antigens, as yet undetermined, might act in the same way in subjects who were not hypersensitive to tuberculin.

However, some facts weigh in favor of the assumption that hypersensitivity to tuberculin, when present, is secondary to recurrent polyserositis in patients who harbor a silent tuberculous focus. Sensitivity to tuberculin belongs to the delayed, cellular type which is neither familial nor genetically determined. In this respect it is interesting to note that one of our patients was highly sensitive to tuberculin, while her son, also affected by the disease, exhibited no reaction to the highest concentrations used. Furthermore, a trial of desensitization failed to influence the course of the disease in one of our cases, although the local skin sensitivity diminished greatly. In view of these facts the exact relationship between hypersensitivity to tuberculin and recurrent polyserositis must await further studies for elucidation.

The development of amyloidosis or polyarteritis nodosa [*32,36*] in some cases of recurrent polyserositis could also be explained on the basis of a hypersensitivity state. Amyloidosis itself is considered to be the result of an immunologic disturbance, apparently involving the deposition of an insoluble glycoprotein product of a local antigen-antibody reaction [*59*].

The nature of the ocular findings in recurrent polyserositis is still unknown. It is interesting to note that we have observed similar white dotted lesions resembling colloid bodies in patients with other immunologic disturbances, such as allergic reactions to penicillin and disseminated lupus. A similar lesion has recently been described in the corpus vitreum of patients suffering from primary familial amyloidosis [*60*]. White dots have also been seen in the retina of these patients, and it has been established that they actually

represent deposits of amyloid. Only one of our four patients with amyloidosis had the fundal lesion, and so far no histologic examinations have been performed.

SUMMARY

The clinical and laboratory features of fifty-five patients with recurrent polyserositis are presented. All patients were Jews, forty-five of Sephardi or Oriental origin, ten of Ashkenazi parentage.

A familial incidence was established in 30 per cent of the families. One generation was affected twice as frequently as two generations.

The symptoms consisted of attacks of fever (all cases), abdominal pain (98 per cent), chest pain (38 per cent), joint pain (31 per cent), gastrointestinal disturbances, headache, and other less frequent manifestations.

The most frequent signs were colloid body-like dots in the eye grounds (50 per cent), palpable spleen (40 per cent), systolic murmur over the apex and parasternally (29 per cent) and palpable (probably enlarged) liver (27 per cent). The main signs during an attack were extreme tenderness and rigidity of the abdominal wall, decreased motility of the diaphragm, and occasional pleural and joint effusion.

The attacks lasted from one to four days, and appeared at irregular intervals of two days to several months. The longest remission (still persisting) was five years. Cold seemed to precipitate, and pregnancy to suppress, the appearance of attacks.

The chief laboratory findings during an attack were leukocytosis, increased sedimentation rate and increased serum α_2 globulin level. An abnormal serum β globulin appeared during an attack in two cases.

Hypersensitivity to old tuberculin was observed in eight of forty-three patients examined. In five of these, attacks could be provoked by the injection of minute quantities of tuberculin. Two of three attempts at desensitization resulted in remissions for as long as eighteen months.

Transient electrocardiographic abnormalities were found in four of thirty-one patients examined. In two of these the changes were suggestive of pericarditis, while in the remaining two the changes were non-specific and confined to the T waves.

Electroencephalographic abnormalities were observed in seven of sixteen patients examined. In two the changes were present only during an attack. The changes were diffuse and non-specific in five, and of the convulsive type in the remaining two.

Amyloidosis developed in four patients (7.2 per cent). Two additional patients had albuminuria without evidence of amyloidosis. Two of the patients with amyloidosis died of renal failure. Autopsy revealed amyloid deposits in the skin, heart, kidneys, skeletal muscle, spleen, ovaries and adrenals.

Except for the patients with amyloidosis, the prognosis was good. The average duration of the disease at the time of the study was nine years and one month. One patient survived more than a thousand attacks in the course of thirty-nine years, with no apparent ill effects on his general condition.

Numerous kinds of treatment were of no avail. ACTH and corticosteroids suppressed the attacks in eleven of fifteen patients, but could not be given indefinitely because of the relatively large doses required, and because the dangers involved were not justified by the temporary nature of the effects.

The pathogenesis of the disease is discussed in the light of present knowledge.

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Clinicopathologic Conference

Ascites and Myelofibrosis

STENOGRAPHIC reports, edited by Lillian Recant, M.D. and W. Stanley Hartroft, M.D., of weekly clinicopathologic conferences held in the Barnes and Wohl Hospitals are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, a white housewife, sixty-five years of age, was admitted to the Barnes Hospital for the first time in July 1960, with the chief complaint of "fluid on my abdomen." She had enjoyed relatively good health until September 1959, when she suffered an influenza-like illness with non-productive cough, muscular aches and pain, malaise and occasional fever. The illness was not accompanied by chills, jaundice, or any change in the character of her stool. Her symptoms persisted virtually unchanged into December 1959, when the cough subsided, but the patient continued to feel tired, and fatigued easily. For these reasons she consulted her private physician who told her she had a large liver and spleen; no specific therapy was recommended. During the ensuing months she noticed swelling of her ankles and increasingly severe shortness of breath. Her appetite was fair and her weight fluctuated a few pounds, depending upon the size of her abdomen. She had no significant nausea or vomiting. On June 28, 1960, an abdominal paracentesis was performed. Approximately 2 to 3 quarts of fluid were removed. The character of this fluid was not known, but no cancer cells were found. During the next few weeks the abdominal fluid reaccumulated, and she was transferred here for further diagnostic study.

The patient's uterus and appendix were removed in 1924. In 1957 an operation was performed for lysis of intestinal adhesions; gallstones were detected, but the gallbladder was left in place. She received one blood transfusion at that time with no reaction, and in the interim had no history of the symptoms of hepatitis. In the 1920's the patient was in an automobile accident and suffered a head injury, following which she noted impairment of the senses of hearing, vision, taste and smell. Normal function had subsequently returned in all senses, except for residual diminution in sense of smell. Review of systems revealed only questionable intolerance to fatty foods. The patient had spent all her life in Illinois. She did not drink or smoke. The only medications she was known to have received were a multivitamin preparation and an unknown pill for her gallstones.

Physical examination revealed a temperature of 37°C.; pulse 90 per minute; blood pressure 110/70 mm. Hg; and respirations 32 per minute. The patient was well nourished, alert, cooperative, and in no acute distress. Examination of the head, eyes, ears, nose and throat was noncontributory. The neck was supple, the thyroid was not enlarged. The chest was symmetrical; respirations were short and rapid. The diaphragm was elevated bilaterally and moved poorly, but no abnormal physical signs were detected over the lung fields. The heart was not enlarged; heart sounds were normal; there were no thrills or murmurs. The abdomen was distended; signs of free fluid were found. The surgical scars of the lower midline were well healed. The liver was palpable as low as the iliac crest; the margin was sharp, firm and minimally tender. The spleen was easily palpable 4 to 6 cm. below the left costal margin and was non-tender. Pitting edema of the feet and ankles (3 plus) and over the sacrum (2 plus) was present. Jaundice, spider angiomas, liver palms, changes in the nail beds, and thickening and contraction of the palmer fascia were not detected. Neurologic examination revealed no abnormalities.

Laboratory data were as follows: hemoglobin 10.2 gm. per 100 ml.; hematocrit 32 per cent; white blood cell count 5,000 per cu. mm.; differential: 1 per cent metamyelocytes, 15 per cent bands, 50 per cent segmented neutrophils, 26 per cent lymphocytes, 8 per cent monocytes; one nucleated red blood cell was seen per 100 white blood cells; reticulocytes 3.3 per cent;

platelets 249,000 per cu. mm. Urinalysis: specific gravity 1.007, reaction 7.0, protein and sugar negative; microscopic examination of the urinary sediment revealed no abnormalities. Stool guaiac and blood Kahn reactions were negative. The cephalin cholesterol flocculation test revealed no abnormalities; other tests were as follows: thymol turbidity 0.8 unit; total serum bilirubin less than 0.8 mg. per cent; albumin 4.3 gm. per cent, globulin 2.3 gm. per cent; alkaline phosphatase 5.5 units; blood urea nitrogen 16 mg. per cent; fasting blood sugar 85 mg. per cent; amylase 84 units; prothrombin time 80 per cent; serum glutamic oxalacetic transaminase 40 units; serum glutamic pyruvic transaminase 15 units; cholesterol 127 mg. per cent; uric acid 8.3 mg. per cent; acid phosphatase 1.9 King-Armstrong units.

Shortly after admission more than 2 L. of clear tannish fluid was obtained by abdominal paracentesis. Specific gravity of this fluid was 1.015; total protein content was 4.2 gm. per cent; cultures and cell blocks were negative. An electrocardiogram was interpreted as showing full atrioventricular conduction, suggestion of an anteroseptal myocardial infarction in the past, sinus tachycardia, low voltage with clockwise rotation. Roentgenograms of the chest and abdomen were interpreted as showing cardiac enlargement, pulmonary congestion, bilateral pleural effusion with interlobar extension, atelectasis of the lower lobe of the left lung, mottled infiltration in the lingula, hepatic enlargement, splenomegaly and radiopaque gallstones. Roentgenographic examinations of the biliary and gastrointestinal tracts demonstrated no esophageal varices, no visualization of the gallbladder, a filling defect of the terminal portion of the duodenum, multiple diverticula of the sigmoid colon, and a filling defect of 1 cm. in the sigmoid colon. Following the abdominal paracentesis, the patient had bilateral costovertebral angle tenderness but no dysuria, frequency or hematuria. Results of cultures of the urine and stool were not significant. Urinary sediment contained only an occasional white blood cell.

On the fifth hospital day retention of bromsulfalein at forty-five minutes was found to be 33 per cent. A surgical consultant, called because no explanation was readily available for the patient's massive ascites and edema, advised abdominal exploration. Serum electrolytes were determined on several occasions preoperatively. (Table I.) On the thirteenth hospital day abdominal paracentesis was repeated. Four hundred milliliters of clear yellow fluid was removed; specific gravity was 1.020; cell block and cultures were negative. The next day the hemoglobin was 10.9 gm. per cent; white blood cell count 9,650 per cu. mm., with a differential of 1 per cent eosinophils, 2 per cent myelocytes, 5 per cent metamyelocytes, 27 per cent bands, 43 per cent segmented neutrophils, 19 per cent lymphocytes, 3 per cent monocytes; there were 2 to 3 nucleated red blood cells per 100 white blood cells; anisocytosis, poikilocytosis, ovalocytosis, and hypochromia of the erythrocytes were described. Urine urobilinogen was negative. On the sixteenth hospital day exploratory laparotomy was performed; 1,600 ml. of clear fluid was aspirated from the abdominal cavity; the liver and spleen were very large. Frozen sections of a biopsy specimen obtained from the liver edge were reported as "extramedullary hematopoiesis." The gallbladder wall was thin and the gallbladder contained gallstones. The kidney and pancreas felt normal in size and consistency. The stomach, duodenum, and small intestine were apparently normal. There was no evidence of elevated portal vein pressure, or of intra-abdominal or retroperitoneal masses. While the patient was on the operating table, bone marrow was removed from the sternum; frozen sections were reported as "myeloid fibrosis." The final surgical pathologic reports were the same as those made on the frozen sections. Postoperatively, the patient's course was marked by one brief episode of an overload of fluid, associated with diminished output of urine and accompanied by edema and increased venous pressure.

TABLE I
SERUM VALUES

Hospital Day	Sodium (mEq./L.)	Potassium (mEq./L.)	Chloride (mEq./L.)	Carbon Dioxide (mEq./L.)	Blood Urea Nitrogen (mg. per cent)
2	...	...	...	...	16
10	129	5.0	97	28.9	...
12	130	5.2	86	26.6	...
13	123	4.1	88	27.9	...
14	126	4.3	86	28.3	26
18	132	6.2	89	28.1	25
19	132	5.8	...	...	...
37	133	5.9	95	22.3	...
39	...	...	...	...	52
40	123	4.1	90	17.3	55
41	130	3.8	92	21.0	...
42	132	4.1	97	22.8	...
43	135	3.3	97	21.2	56
45 (A.M.)	138	6.6	106	21.2	58
45 (P.M.)	...	9.0	...	...	...

Reaccumulation of abdominal fluid required repeat abdominal paracentesis on the sixteenth postoperative (thirty-second hospital) day.

A consultant in hematology obtained the following peripheral blood data: erythrocyte count 2.83 million per cu. mm., hemoglobin 9 gm. per cent, reticulocytes 6 per cent, platelets 183,000 per cu. mm., white blood cell count 5,400 per cu. mm. The differential on 100 cells was 2 basophils, 1 promyelocyte, 5 myelocytes, 2 metamyelocytes, 26 bands, 39 segmented neutrophils, 17 lymphocytes, 8 monocytes; 2 nucleated red blood cells per 100 leukocytes; marked poikilocytosis with many teardrop-shaped cells. A diagnosis of myeloid metaplasia was made; treatment to reduce the size of the liver and spleen (with bisulfan) and to stimulate hematopoiesis (with testosterone) was recommended.

Before operation the patient had been digitalized; maintenance doses of digitalis were given postoperatively. She still, however, complained of episodic dyspnea. The house officers were not certain whether these episodes were associated with anxiety and the distress caused by the massive accumulation of ascitic fluid, or whether they represented congestive heart failure. She also complained at times of vague pain along the left costal margin and over the precordium.

On the thirty-third hospital day the patient was returned to the medical service. She had massive ascites, but the lungs were clear. The neck veins were distended even in the sitting position, and there was 2 plus edema of the lower extremities. During the next few days her mental attitude changed. At times she was quarrelsome and seemed to be disoriented; periodically she was confused. The administration of digitalis was continued and a low-salt diet was prescribed. Attempts at diuresis with mercurial diuretics, ammonium chloride and acetazoleamide were only partially successful. On the thirty-seventh hospital day serum electrolyte and hepatic function tests were repeated. (Table I.) On the same day a diagnostic abdominal paracentesis was performed. Only 20 ml. of clear, straw-colored fluid was removed, which clotted after standing. The protein content was 3.7 gm. per cent; the cell count was 300 cells per cu. mm. without acid, O cells with acid; cultures, both routine and for acid-fast bacilli, were negative; smear for acid-fast bacilli was negative. Roentgenographic examination of the chest demonstrated prominent pulmonary vasculature with pulmonary edema, bilateral pulmonary effusion, very small localized left pneumothorax. Venous pressure was 230 mm. of saline; circulation time, arm-to-tongue (Decholin®), was twenty-three seconds. Prothrombin time was 48 per cent. Hemoglobin was 9.7 gm. per cent; white blood cell count, 12,150 per cu. mm.

An electrocardiogram on the thirty-eighth hospital day was interpreted as showing anteroseptal myocardial infarction in the past as noted before; diaphragmatic myocardial infarction of uncertain duration (in retrospect, also noted on previous tracings); coupled rhythm, with a nodal escape beat following a non-conducted sinus beat and followed by a conducted atrial premature contraction; effect of digitalis, question of excess; full atrioventricular conduction. The following day a sinus arrhythmia was detected. Blood urea nitrogen was found to be 52 mg. per cent. A clean voided specimen of urine grew out confluent E. coli, protein trace, sugar negative; microscopic examination of the centrifuged urinary sediment revealed 25 to 30 white blood cells per high power field. From days thirty-six to forty, the patient's temperature (otherwise always normal) was elevated to between 38° and 39°C.

Treatment was begun with tetracycline, to which the infecting organism proved sensitive *in vitro*. On the fortieth hospital day an electrocardiogram was unchanged. White blood cell count was 5,400 per cu. mm., with a differential of 3 per cent myelocytes, 1 per cent metamyelocytes, 15 per cent bands, 67 per cent segmented neutrophils, 13 per cent lymphocytes, 1 per cent monocytes; the hemoglobin was 8.6 gm. per cent; platelets were questionably decreased on the blood film. Administration of bisulfan was temporarily discontinued. The infection of the urinary tract responded very promptly to treatment with tetracycline. At the same time, slight diuresis occurred, and the patient seemed to be improving. Two days later the white blood cell count was 4,200, with a differential of 13 per cent bands, 69 per cent segmented neutrophils, 17 per cent lymphocytes, 1 per cent monocytes; one nucleated red blood cell was seen per 100 white blood cells; the hemoglobin was 8.6 gm. per cent. Urinalysis revealed a specific gravity of 1.006, reaction 6.5, protein trace, sugar negative; microscopic examination of the centrifuged urinary sediment revealed bacteria, renal cells,

epithelial cells, amorphous precipitate, and 2 to 3 granular casts per high power field. An electrocardiogram was unchanged except for prolongation of the P-R interval. A vectorcardiogram revealed anteroseptal and diaphragmatic myocardial infarction. Oral supplementary potassium therapy was begun.

On the forty-fourth hospital day the urine sediment was non-contributory, hemoglobin 8 gm. per cent, platelets 72,100 per cu. mm. Erythrocyte sedimentation rate (corrected) was 17 mm. per hour. The patient's physical examination was largely unchanged; there were persistent ascites and edema, some rales present in both lung fields, distended neck veins, dyspnea and tachypnea.

The next day, shortly after administration of a unit of packed red blood cells was begun, the house officer was called because the pulse rate was found to be 44 per minute. Results of blood chemical determinations made earlier during the day were as follows: sodium 138 mEq. per L.; potassium 6.6 mEq. per L.; CO_2 21.2 mEq. per L.; chloride 106 mEq. per L.; blood urea nitrogen 58 mg. per cent. The blood pressure was 110/70 mm. Hg, temperature was normal, pulse was 44 per minute and regular. The lungs were clear. The heart sounds were distant without rubs or gallop. An electrocardiogram revealed an idioventricular rhythm with a rate of approximately 48 per minute. The patient did not seem to be in any distress from the slow heart rate. For this reason no specific therapy was given, but the serum potassium was determined and found to be 9 mEq. per L. The patient had received approximately 350 mEq. of oral supplemental K^+ to this time. Urine output had always been greater than 1,500 ml. per day. About two hours after the onset of bradycardia, the physical examination was unchanged; the pulse rate was approximately 48 per minute, the blood pressure was 100/60 mm. Hg. A repeat electrocardiogram revealed persistent idioventricular rhythm; no P waves could be identified; the QRS was spread widely; there were high, peaked T waves. While the house officer was present the patient vomited several times, each time bringing up only a small amount of brown liquid material. Administration of the unit of packed red blood cells had by now been completed; infusion of dextrose and water was begun. Approximately a half hour later the patient had cyanosis and apnea. In spite of the use of a cardiac pacemaker and Bennett respirator, no response could be obtained. During the resuscitation procedures the patient vomited a small amount of brownish material one time and seemed to aspirate a portion of the vomitus. At 12:10 A.M. on the forty-sixth hospital day she was pronounced dead.

CLINICAL DISCUSSION

DR. CARL V. MOORE: The hematologic changes in this woman's peripheral blood and bone marrow were consistent with a diagnosis of myeloid metaplasia and myelofibrosis. The known duration of her illness, less than one year, was surprisingly short for this syndrome, but postoperatively manifestations of cardiac failure and of renal insufficiency developed. The terminal episode was apparently related to hyperkalemia.

Mr. Hurwitz will discuss the roentgenograms.

MR. ARYEH HURWITZ: Roentgenograms of the chest on admission showed the heart to be markedly enlarged. Fluid was present in both costophrenic angles extending up to the scapula on the left and into the intralobar fissure on the right. The aorta was lengthened, and the hilar regions were hazy. The pulmonary vascular markings extended to the periphery, indicating pulmonary congestion. The diaphragms were elevated, and moved poorly. On the lateral film, atelectasis of the lower lobe of the left lung, increased pulmonary markings, and cardiomegaly was observed.

An abdominal film showed that the spleen extended within a half inch of the iliac crest; calcified stones were present in the area of the gallbladder; the bony structure was non-contributory. Examination of the gastrointestinal tract revealed diverticula of the sigmoid colon, and spasticity consistent with diverticulitis. The filling defect in the sigmoid colon was probably a diverticulum with feces. There was a filling defect in the transverse colon. The kidneys were not seen clearly, but appeared to be normal in size and shape. A barium study of the esophagus was within normal limits. The stomach and the proximal duodenum were normal. There was a filling defect of the terminal portion of the duodenum, with irregularity of the mucosa, consistent with an intraluminal mass of some sort.

Roentgenograms taken on the thirty-third hospital day showed more enlargement of the heart, persistence of the pleural effusions and increased pulmonary congestion.

DR. MOORE: What are your final diagnoses?

MR. HURWITZ: Cardiomegaly, pulmonary congestion, pleural effusion, filling defects in the duodenum and transverse colon, non-visualizing gallbladder with radiopaque gallstones, massive ascites with poor motion of the diaphragm, and hepatosplenomegaly.

DR. MOORE: Mr. Cooper, since we have firm pathologic diagnoses of myelofibrosis in the bone marrow and extramedullary hematopoiesis in the liver, we probably should begin by discussing myelofibrosis. How do you think myelofibrosis should be classified?

MR. RICHARD COOPER: The classification of generalized myelofibrosis might begin with agnogenic, idiopathic or primary myelofibrosis. In addition, the syndrome may be secondary to toxic factors such as benzene, fluorine or radiation. This condition is seen secondary to other hematopoietic diseases, such as polycythemia and myeloma, and to such infiltrative diseases as carcinoma, lymphoma and Gaucher's disease. Amyloidosis has also been mentioned as a cause.

DR. MOORE: When a patient has myelofibrosis secondary to infiltrative disease from a carcinoma, for instance, is the myelofibrosis then generalized or does it tend to be localized?

MR. COOPER: Although the metastases may involve only small portions of the bone marrow, the fibrosis may involve significantly larger portions of the bone marrow and may indeed be generalized.

DR. MOORE: Mr. Birge, would you continue the discussion by telling us briefly your concept of the pathogenesis of myelofibrosis, starting with the primary or idiopathic variety and then trying to relate that to what is known about the causation of the secondary forms of myelofibrosis.

MR. CLIFFORD A. BIRGE: I do not think the cause of either primary or secondary myelofibrosis is understood.

DR. MOORE: I had hoped you would discuss briefly your reaction to the suggestion that myelofibrosis is not a separate entity, but a manifestation of a myeloproliferative disorder.

MR. BIRGE: Because there is considerable overlapping in the picture of polycythemia, myelofibrosis and chronic myelocytic leukemia, Dameshek* and some other authors tend to put these entities together. However, it is my belief that there are enough distinctive characteristics that they should be categorized separately.

* DAMESHEK, W. Some speculations on the myeloproliferative syndrome. *Blood*, 6: 372, 1951.

DR. MOORE: The suggestion has been made, Mr. Birge, that myelofibrosis might originate in areas in which there is necrosis of bone marrow cells, with fibrosis being a reaction to the necrosis. Does this concept have too flimsy a basis for you?

MR. BIRGE: Yes.

DR. MOORE: As Mr. Birge has implied, many students regard myelofibrosis as one manifestation of a myeloproliferative syndrome, whereas other persons believe it to be a distinctive entity; there is probably no point in continuing this discussion because we cannot possibly resolve the difference of opinion.

Mr. Graber, one of the most interesting aspects of this patient's course was the early onset of ascites. Is this not unusual in myelofibrosis, and how would you explain it?

MR. ALAN L. GRABER: The manifestation of ascites without any other explanation was indeed unusual in this disease. In one series, ascites was only seen in two of fifty-six cases,* unless there were other reasons for the ascites. Unless there are areas of myeloid metaplasia in the liver, perhaps compressing the hepatic vein or compressing the superior vena cava proximal to the liver, we will have to look for other explanations of the ascites.

DR. MOORE: Does anyone have any other explanation for the ascites?

MR. COOPER: In answering the question a few minutes ago on the causes of myelofibrosis, I did omit one etiology, tuberculosis. Tuberculosis, with miliary spread, could be responsible for myelofibrosis and pleural effusion.

DR. MOORE: I suppose any one of the infectious granulomas could be included.

MR. NICHOLAS KOUCHOUKOS: Congestive heart failure in this woman seems the most logical explanation for the onset of her ascites.

DR. MOORE: Mr. Graber, did you happen to read a paper by Dr. Oishi and his associates† on ascites in myelofibrosis?

MR. GRABER: No sir, I did not.

DR. MOORE: These authors postulate that increased forward blood flow through the splenoportal system may be a factor in the pathogenesis of the portal hypertension which occasionally occurs in myeloid metaplasia.

* LINMAN, J. and BETHELL, F. Agnogenic myeloid metaplasia. *Am. J. Med.*, 22: 107, 1957.

† OISHI, M., SWISHER, S. N., STORMONT, J. M. and SCHWARTZ, S. I. Portal hypertension in myeloid metaplasia. *Arch. Surg.*, 81: 80, 1960.

According to this concept, portal hypertension may occur in the absence of hepatic congestion or periportal fibrosis simply because the flow of blood in the portal vein is so great.

Mr. Finkelstein, the manifestations of myelofibrosis include anemia, occasional thrombocytopenia, thromboses, hepatomegaly, splenomegaly and bone marrow change. What other organs may be involved?

MR. HARVEY FINKELSTEIN: Myeloid metaplasia may involve the kidneys, possibly the adrenal glands, and in some cases even the lung.

DR. MOORE: May extramedullary hematopoiesis in the kidney be great enough to cause renal insufficiency?

MR. FINKELSTEIN: Probably not. Dr. Castleman* believes that it is most unusual for the cellular infiltration associated with myeloid metaplasia to disrupt function of any organ.

DR. MOORE: What about extramedullary hematopoiesis in cardiac muscle?

MR. FINKELSTEIN: That must be an extremely rare occurrence.

DR. MOORE: It occasionally will be found, but I am not aware of instances in which the degree of extramedullary hematopoiesis in the myocardium has been great enough to induce heart failure.

MR. WILLIAM T. BRAUN: Within the last year, Dr. James Pitcock and Dr. Edward H. Reinhard have reviewed sixty-three cases of idiopathic myelofibrosis and twenty-eight cases of the secondary type from the records of the hematology service here. Bone marrow studies were made in all these cases; the amount of estimated fibrosis varied from 22 to 55 per cent. There was also a variable appearance in the marrow of the patients who had secondary myelofibrosis.

Dr. Pitcock found that fibrosis was very widespread in this disease, and postulates a generalized fibrotic process involving all the organs, but mainly the bone marrow and the spleen. Fibrosis was also found in the liver, pancreas, lungs, mediastinum and heart. It was also found in the kidneys, producing a renal disease, mainly of the obstructive type. In this series, involvement of the kidney was much more frequent than has previously been reported. It should be emphasized, however, that in no case was the extramedullary fibrosis sufficient to produce any symptoms.

DR. MOORE: These comments are pertinent to the rest of our discussion, because now we must go on to a consideration of the cardiac lesions in this patient, then to the renal lesion. Mr. Braun, will you discuss the electrocardiograms?

MR. BRAUN: There were several non-specific changes in the electrocardiogram taken on admission such as low voltage, marked left axis deviation and clockwise rotation. In addition, prolonged A-V conduction time, T wave abnormalities and an abnormal form of ventricular complex were found. The anterior septal myocardial infarction read on these electrocardiograms cannot really be documented too well, especially in the presence of left axis deviation and a clockwise rotation. The records taken until the day of death were much the same as the first one. The diaphragmatic infarction also read cannot be definitely documented. The electrocardiogram taken shortly before death, when presumably the serum potassium was quite elevated, showed elevated T waves, low R waves, absence of the P waves and widening of the QRS complex. These changes were compatible with hyperkalemia, which is also a fairly good explanation for her death.

DR. MOORE: What should the differential diagnosis of the cardiac lesion include?

MR. JOHN BALFOUR: This patient had congestive failure and cardiomegaly. At her age, you would think along the lines of arteriosclerotic heart disease. However, she did not have a past history suggestive either of angina or myocardial infarction.

DR. MOORE: But the electrocardiographic changes were initially interpreted as being compatible with myocardial infarction.

MR. BALFOUR: I meant clinical manifestations. Even so, that diagnosis must seriously be considered. Myocarditis can also cause congestive failure with an enlarged heart. If you were considering myocarditis, you would be most prone to think of Fiedler's myocarditis with idiopathic interstitial fibrosis. The other types of myocarditis rarely cause congestive heart failure unless they are of rheumatic nature. You would also have to consider pericarditis.

DR. MOORE: Do you really mean that the myocarditis of influenza, for instance, and of other virus infections, will not give you cardiac failure?

MR. BALFOUR: Friedberg states that cardiac failure occurs only occasionally as a result of myocarditis alone, except in rheumatic fever. He does say that other forms of myocarditis, as in

* Case Records of the Massachusetts General Hospital. *New England J. of Med.*, 256: 1112, 1957.

viral infections, can give cardiac failure; but I think it is unusual.

DR. MOORE: Is it conceivable to you that the illness the patient had beginning in September 1959 was a viral infection which led to myocarditis of this duration?

MR. BALFOUR: I think it is a very good possibility.

DR. MOORE: The time interval was not too long?

MR. BALFOUR: I do not think so.

DR. MOORE: That would seem most unusual to me.

MR. BALFOUR: Pericarditis would have to be entertained. You would also have to consider infiltrative diseases, such as amyloidosis, a diagnosis that often can be suspected only by excluding other possibilities. The electrocardiographic findings were compatible with amyloidosis. The syndrome of idiopathic hypertrophy of the heart was still another possibility here.

DR. MOORE: The suggestion was made, by Mr. Cooper I believe, that amyloid disease may have caused an infiltrative lesion of the bone marrow leading to myelofibrosis; now Mr. Balfour suggests that amyloid may have been responsible for the infiltrative lesion in the myocardium. If this patient did have amyloid disease, what kind would it be?

MR. GERALD A. WOLFF: The primary type of amyloidosis more characteristically affects the heart; if we postulated amyloid heart disease, we would expect primary amyloidosis.

DR. MOORE: And what other organs are involved with primary amyloid disease?

MR. WOLFF: Characteristically, the skin and skeletal muscles are involved.

DR. MOORE: You do not believe that we could explain the renal manifestations on the basis of amyloid disease?

MR. WOLFF: It would be unusual.

DR. MOORE: Mr. Oppenheimer, are you in agreement with this? I was under the impression that primary amyloid disease involves the liver, kidneys and other tissues much more frequently than we formerly thought.

MR. STEVEN OPPENHEIMER: Although the classification was originally made with the thought that primary amyloidosis chiefly involves the tissues mentioned by Mr. Wolff, and that the secondary form involves mainly the reticuloendothelial system and the kidneys, this sharp differentiation does not hold. "Primary amyloidosis" may involve the kidneys, spleen and liver; the secondary form may involve the heart and skeletal muscles.

DR. MOORE: You are inclined, however, to agree that if this was amyloid disease, it was primary and may have affected the kidneys?

MR. OPPENHEIMER: That is the more likely possibility.

DR. MOORE: Mr. Kouchoukos, do you care to suggest any other causes for the renal disease? This patient's urinary output remained satisfactory until the time she died. Her blood urea nitrogen did not rise until terminally; it did not begin to rise until after she had what was apparently a rather acute infection of the lower urinary tract during the last several weeks of life. The infection responded fairly well to therapy. Do you have any other suggestions as to why there was a terminal rise in blood urea nitrogen and potassium?

MR. KOUCHOUKOS: The most likely answer would be the onset of an acute episode of pyelonephritis in the period shortly before she died. We had no history of any previous renal disease. The roentgenograms showed no gross evidence of chronic renal disease. We might have expected the kidneys to be enlarged if they were infiltrated with amyloid. Certainly another thing to be considered, as has already been mentioned, was the possibility of extramedullary hematopoiesis in this organ, which possibly might have caused some decompensation of function. The overt heart disease could have also compromised the function of the kidney and account for the rise in blood urea nitrogen.

DR. MOORE: Which one diagnosis would you select as the most likely explanation for her terminal renal involvement?

MR. KOUCHOUKOS: Congestive failure.

DR. MOORE: Congestive failure, plus the . . .

MR. KOUCHOUKOS: . . . superimposed pyelonephritis, terminally.

DR. MOORE: Mr. Finkelstein, did you have any comment to make?

MR. FINKELSTEIN: The persistently elevated uric acid might have resulted in the deposition of uric acid crystals in the kidney.

DR. MOORE: Very good. Mr Crosson, will you discuss the rather sudden terminal elevation in serum potassium. Was the transfusion responsible for the rather acute rise in her potassium, from 6 to 9 mEq.? Was the oral supplementation of the potassium responsible? If your answer is "yes," why was it responsible, since her urinary output remained so good?

MR. JOHN T. CROSSON: First, I believe Dr. Peden told us yesterday that the blood this patient received was only four days old, and was given as packed cells, not whole blood.

DR. MOORE: Why were packed cells used?

MR. CROSSON: To avoid circulatory overload in a patient with congestive failure. There was also evidence of hyperkalemia prior to the transfusion.

DR. MOORE: What is the potassium content of the plasma in blood which has been kept in a blood bank for four days?

MR. CROSSON: The potassium content of the plasma at that time could be 8 or 9 mEq. per L., I believe.

DR. MOORE: At the end of ten days of storage, the plasma content of A.C.D blood may be 15 mEq. per L. I am not sure what the level would be at four days, but it would be lower than that figure.

MR. CROSSON: We have evidence that this patient had a very good renal output up until the day of her death. However, she had a persistent hyponatremia throughout her course, and she also had acidosis. These changes would increase the toxic effects of hyperkalemia. Also, the episode of acute pyelonephritis could have involved the tubular part of the kidney specifically. I think we have reason to believe that she might have had difficulty excreting a potassium load, in spite of the persistently good urinary output.

DR. MOORE: We do not necessarily have to postulate specific destruction of potassium excreting sites. I think we may assume that the patient had a decreased population of functioning nephrons which were probably excreting potassium at a maximum rate and were unable to increase this rate in response to a further potassium load.

Any additional suggestions from anyone? Now Mr. Cooper, you started out by telling us that myelofibrosis could be primary or secondary. Will you close our discussion by stating your final opinion. Do you think this woman had primary myelofibrosis with an additional cardiac lesion, as for instance coronary artery disease or myocarditis, or was the myelofibrosis secondary?

MR. COOPER: In view of the laparotomy and biopsy specimen of the liver, which showed no secondary lesion, and the absence of enlarged lymph nodes or signs of other disease, I think we are forced to say that this was primary myelosclerosis with myeloid metaplasia. I think we are given two alternatives concerning the heart. We can go along with Dr. Pitcock and Dr. Reinhard's suggestion of a generalized sclerosis which involved many organs in the body, and indeed involved the heart. We were able to find only one patient described in the literature with a similar complex and her cardiac function was not seriously disturbed, although it certainly is conceivable that fibrosis could be more extensive in the patient today and could have compromised her cardiac function. The other suggestion of amyloid disease of the heart, whether or not it involved the kidneys, is more appealing. This patient was sixty-five years old; certainly amyloid disease involving the heart alone is being recognized more frequently in older people, usually over the age of seventy.

DR. MOORE: That is an excellent summary of the possibilities. I would like to take a vote on two things. How many of you would go along with Mr. Cooper's suggestion that this was primary myelofibrosis, rather than secondary? There is unanimous agreement. From this point on we have to guess, because this patient could have had coronary artery disease, fibrosis, amyloid disease or myocarditis. We are just not in possession of the necessary data to make this differentiation. How many of you vote in favor of coronary artery disease? Three. How many for myocarditis? One. How many for just diffuse fibrosis? One. How many for amyloid disease? Five. I do not quite understand why, if you make the diagnosis of amyloid disease of the heart, you do not extend this and say that amyloidosis might have caused the myelofibrosis as well.

PATHOLOGIC DISCUSSION

DR. ROBERT HEPTINSTALL: This patient showed many interesting features and it would be well to mention these very briefly. We have called this a myeloproliferative disorder, with hyperplasia of the marrow cells, particularly of the myeloid and megakaryocytic series. There was, in addition, focal myelofibrosis and myelosclerosis of the bone marrow. We have preferred to use this general descriptive term myeloproliferative disorder, rather than such terms as agnogenic myeloid metaplasia and myelosclerosis, because it is important to call attention to the fact that there was hyperplasia of many elements in the bone marrow. There was considerable extramedullary hematopoiesis, particularly in the spleen, which was very large and weighed 1,300 gm., while lesser degrees of hematopoiesis

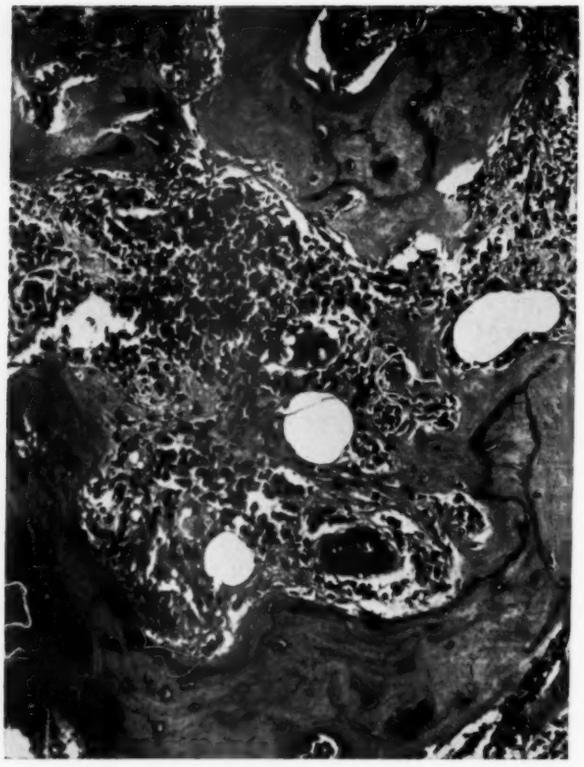

FIG. 1. Bone marrow to show new bone formation. Mild fibrosis and presence of blood forming cells. Hematoxylin and eosin stain, magnification × 120.

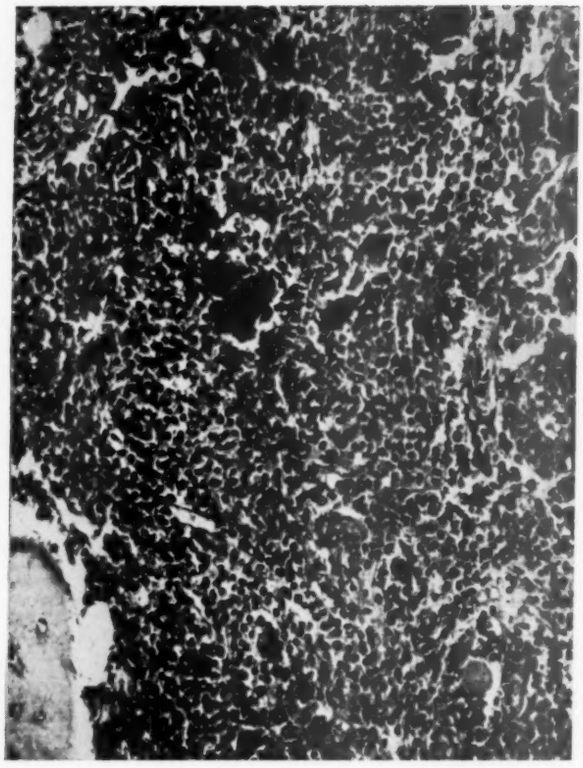

FIG. 2. Bone marrow to show hyperplasia of blood forming cells. Megakaryocytes prominent. Hematoxylin and eosin stain, magnification × 180.

were found in the liver, lymph nodes, kidney, lungs and ureters. Hemosiderosis of the spleen, lymph nodes and liver was quite a striking change, and it is rather surprising that serum bilirubin values were consistently low. Amyloid was present particularly in the heart and to a lesser degree in the liver, spleen, kidney, ureters and lymph nodes. Finally, there was an extremely severe acute pyelonephritis, particularly affecting the left kidney.

In the vertebrae, ribs, sternum and ilium there were areas of dense fibrosis, but this was essentially a patchy process and large areas were spared. Considerable new bone formation was also present, this change again being patchy. (Fig. 1.) In addition, however, there was a very pronounced hyperplasia of the blood-forming cells (Fig. 2) and this is important considering some of the views that have been expressed about myelosclerosis, particularly those in which the disease is considered to be purely an obliteration of the marrow with compensatory extramedullary hematopoiesis. Megakaryocytes were the most prominent cells, but myeloid and erythroid cells also took part in the proliferation.

The spleen was soft and very large, weighing 1,300 gm. It was uniformly red except for a slightly paler nodule which histologically showed more proliferation than the rest of the organ. Sections showed considerable hematopoiesis with large numbers of megakaryocytes. (Fig. 3.) Some fibrosis was also seen and there was a large amount of hemosiderin in macrophages. Lymph nodes contained megakaryocytes and some showed so much hemosiderin as to give them a reddish tinge. The liver showed megakaryocytes but in greatly reduced numbers compared with the biopsy specimen taken three weeks before death. Pigment stones were found in the gallbladder.

This patient's terminal renal trouble, was a rather severe acute pyelonephritis, the left kidney being more severely affected than the right. Minor degrees of hematopoiesis were seen in areas away from the infection.

The heart showed rather dramatic changes in the form of extensive amyloid infiltration, particularly of the mitral valve and endocardium of the left atrium. Histologically the main deposits were in the sites seen grossly (Fig. 4),

but they were also present in the endocardium and myocardium of the other chambers. The heart was surprisingly small (330 gm.) in view of the presence of congestive failure.

Most of the organs showed a mild degree of involvement by amyloid. It is worth speculating whether or not the amyloid which was present in the ureter could have interfered with the movements of the ureter and so predisposed to the pyelonephritis.

The main anatomic diagnoses were myeloproliferative disorder; hyperplasia of marrow cells, particularly myeloid and megakaryocytic series; focal myelofibrosis and myelosclerosis; extramedullary hematopoiesis of spleen, liver, lymph nodes, kidney, lungs and ureters; hemosiderosis of spleen, lymph nodes and liver; generalized systemic amyloidosis affecting particularly the heart; acute pyelonephritis.

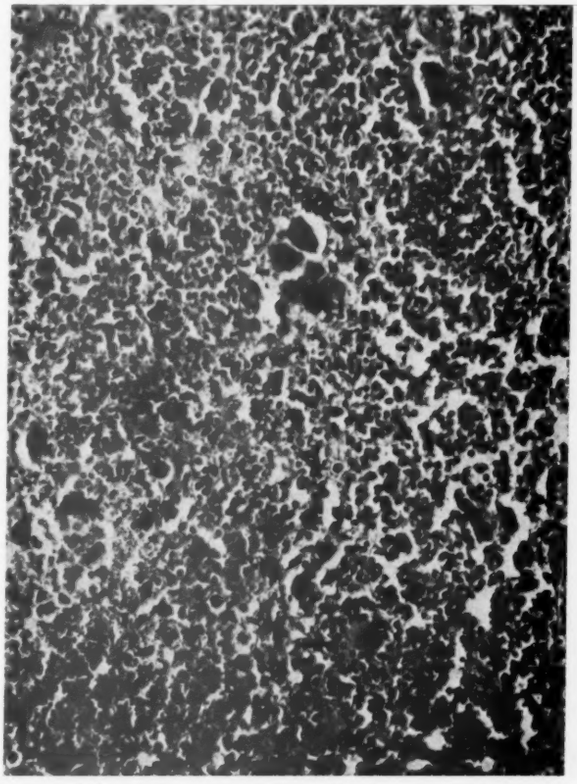

FIG. 3. Spleen to show extramedullary hematopoiesis with large numbers of megakaryocytes. Hematoxylin and eosin stain, magnification × 140.

DISCUSSION

DR. MOORE: Can you tell us whether or not there was amyloid in the marrow?

DR. HEPTINSTALL: There was no amyloid in the marrow as far as we could see.

DR. MOORE: One thing was omitted from the discussion. Teardrop cells were recognized in this woman's blood, and because of the teardrop cells the diagnosis of myelofibrosis was suspected. This morphologic change in erythrocytes is well worth remembering.

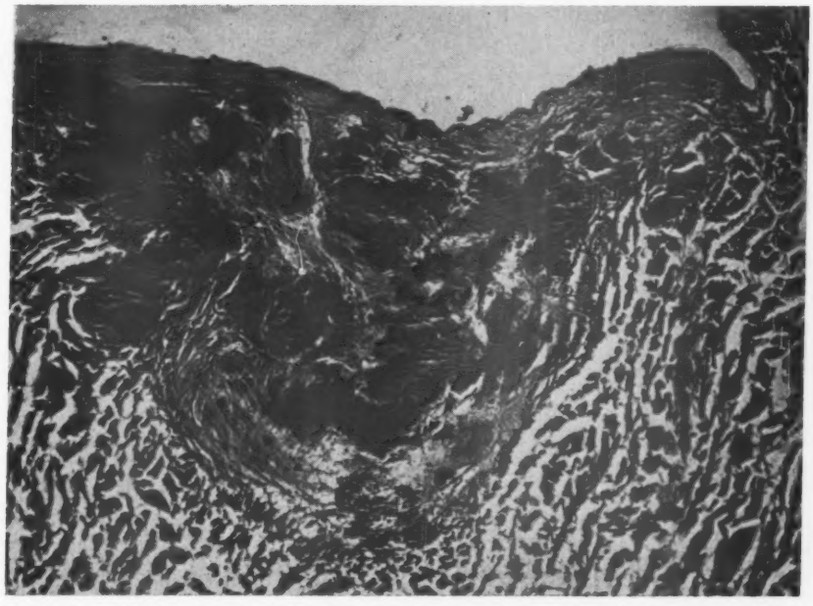

FIG. 4. Amyloid deposit in mitral valve. Hematoxylin and eosin stain, magnification × 140.

Case Reports

Interstitial Pulmonary Fibrosis Following Busulfan Therapy*

HERMAN OLINER, M.D.,† ROBERT SCHWARTZ, M.D.,† FERNANDO RUBIO, JR., M.D. *and* WILLIAM DAMESHEK, M.D.

Boston, Massachusetts

BUSULFAN (1–4, dimethanesulfonoxybutane) (Myleran®) was introduced in the treatment of chronic granulocytic leukemia in 1953 by Haddow and Timmis [*1*]. Since then it has found wide application in the therapy of this disease and is now considered by many to be the treatment of choice. When properly used the drug induces a high remission rate in patients with chronic granulocytic leukemia; complications due to myelotoxicity are infrequent and the majority of these patients are rapidly restored to a state of good health [*2*]. The principal hazard arising from its use is aplasia of the bone marrow; this is generally related to overdosage, although in a few patients it ensues after a relatively small dose and appears to be the result of unusual sensitivity to the drug. A common feature of busulfan therapy is hyperpigmentation of the skin [*3*]. This eventually develops in many patients treated for periods of two years or longer. The mechanisms for the development of the pigmentation are quite obscure but seem to be unrelated to involvement of vital organs.

Recently we have observed two patients with a hitherto undescribed complication during busulfan therapy, namely interstitial pulmonary fibrosis. The purpose of this paper is to describe these patients and to comment on the possible significance of this complication.

CASE REPORTS

CASE 1. W. E. (New England Center Hospital No. 110–173), a fifty-seven year old male geologist, was seen in February 1957 because of weight loss and weakness. He was found to have the typical blood and bone marrow features of chronic granulocytic leukemia. Busulfan therapy was begun on February 7, 1957; initially he received 12 mg. daily, and this was gradually reduced to a maintenance dose of 2 mg. per day. The hepatosplenomegaly and leukocytosis initially present resolved and he became symptom-free. Nine months later, in November 1957, however, he complained of dyspnea, cough, fever and weakness. He was treated at home, with several antibiotics but failed to improve. When hospitalized in December 1957, he appeared chronically ill; his rectal temperature varied between 100°F. and 101.6°F. Examination of the lungs disclosed diffuse fine rales which cleared on coughing. The remainder of the physical examination was within normal limits. There was neither cyanosis nor clubbing. The laboratory data were: hemoglobin 8 gm. per cent, hematocrit 30 volumes per cent, red blood cells 2.9 million per cu. mm., reticulocytes 2.8 per cent, platelets 852,000 per cu. min., white blood cells 9,600 per cu. mm. with 89 per cent polymorphonuclear leukocytes, 6 per cent lymphocytes, 1 per cent monocytes, 2 per cent eosinophils, 1 per cent basophils and 1 per cent metamyelocytes. The erythrocyte sedimentation rate was 110 mm. in the first hour. Bone marrow was easily aspirated from the iliac crest, and on examination showed hyperplasia of the granulocytic series. The serum total proteins were 5.4 gm. per cent with 2.2 gm. per cent albumin and 3.2 per cent globulin (in February 1957, the serum total proteins were 6 gm. per cent with 3.5 gm. per cent albumin and 2.5 gm. per cent globulin). Blood, urine and sputum cultures were negative for pathogens.

The roentgenogram of the chest showed a remarkable change from the previous normal film of February 1957. Bilateral diffuse mottled densities were now present, suggesting an inflammatory process. (Fig. 1.) Results of skin tests for tuberculosis, histoplasmosis and coccidioidomycosis were negative. The administration of busulfan was discontinued and the patient was

* From the Blood Research Laboratory, a unit of the Ziskind Laboratories, New England Center Hospital and the Department of Medicine, Tufts University School of Medicine. This study was aided by a grant from the U. S. Public Health Service (National Cancer Institute) Contract No. CY–4168.

† U. S. Public Health Service Fellow.

discharged from the hospital without a definite diagnosis.

One month later he was readmitted because of increasing dyspnea and fever. The findings on physical examination were unchanged. The blood counts did not differ significantly from those of the previous admission. Sputum cultures failed to grow pathogenic bacteria or fungi. Two cultures of the gastric contents for acid-fast bacilli were negative. The roentgenogram of the chest now showed the pulmonary infiltrates to be most prominent in the right middle and upper lobes and in the left lower lobe of the lung. Bronchoscopy demonstrated redness and thickening of the mucosa of the middle lobe bronchus. Again, cultures of the sputum, blood, urine, and bronchoscopic and gastric washings, were negative for pyogenic and acid-fast bacteria and fungi. A biopsy specimen of a scalene node produced a normal lymph node.

Biopsy of the right lung showed extensive, focal interstitial chronic pneumonitis with fibrosis and pleural adhesions. (Fig. 2.) The predominant feature of the process was interstitial fibrosis, the inflammatory exudate was scanty and consisted of lymphocytes and plasma cells. The bronchiolar and alveolar walls were conspicuously lined by proliferating alveolar or septal cells which were atypical in appearance. A rare focus of calcification was seen. No evidence of leukemic infiltration was found. In addition, a chronic proliferative form of endarteritis was present. (Fig. 3.) The most striking change was in the arterioles, which showed sclerosis of the walls and focal inflammation. Occasional blood vessels were partly or completely occluded by organizing thrombi.

In view of the possibility that the pulmonary syndrome represented a hypersensitivity reaction to busulfan, therapy with corticosteroids was begun. Prednisone was given in a dosage of 50 mg. per day initially; this was gradually reduced and finally discontinued two months later. Within one month

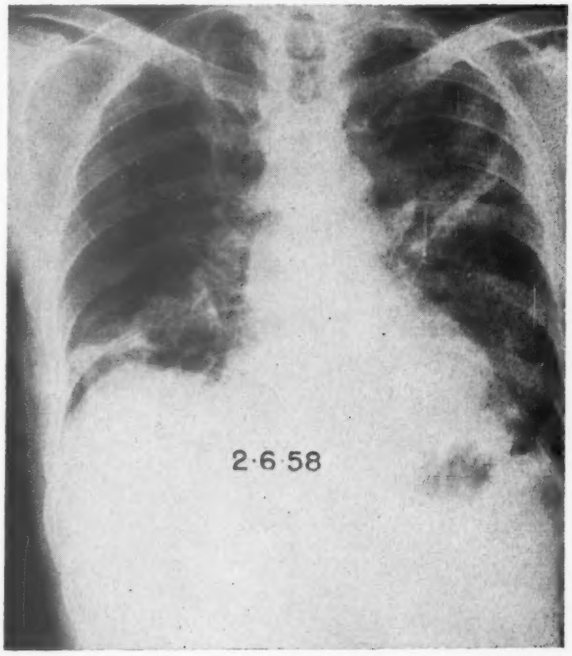

FIG. 1. Roentgenogram of the chest in Case 1 taken on admission. Bilateral mottled densities and linear infiltrates are present.

there was a striking clinical and radiologic improvement. (Fig. 4.) The dyspnea, cough and weakness disappeared promptly, there was a gain of weight, and the patient felt much improved. In April 1958, an increased number of myeloblasts was found in the peripheral blood. These cells gradually became more and more numerous, and in July 1958, busulfan therapy was reinstituted. The busulfan was given continuously for the next fifteen months, with considerable improvement in the peripheral blood findings. Despite the reinstitution of busulfan there was no

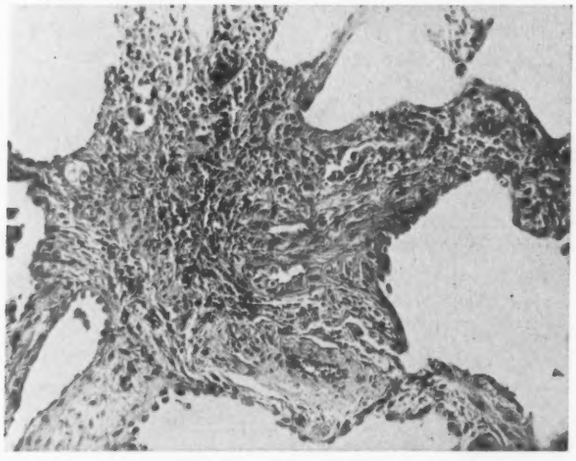

FIG. 2. Photomicrograph of a biopsy specimen of the lung in Case 1, showing extensive, focal interstitial chronic pneumonitis with fibrosis, × 100.

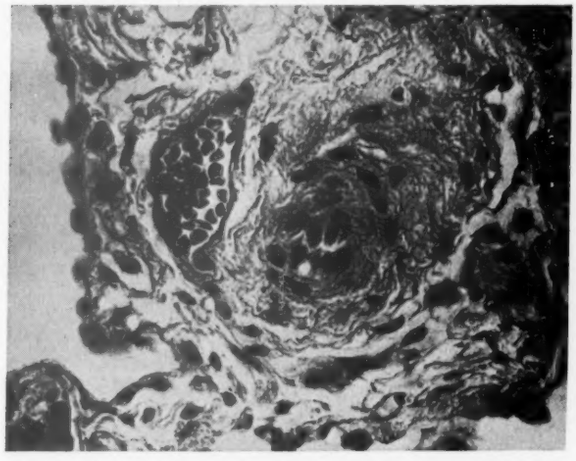

FIG. 3. Photomicrograph of a biopsy specimen of the lung in Case 1 demonstrating marked proliferative endarteritis without inflammation, × 440.

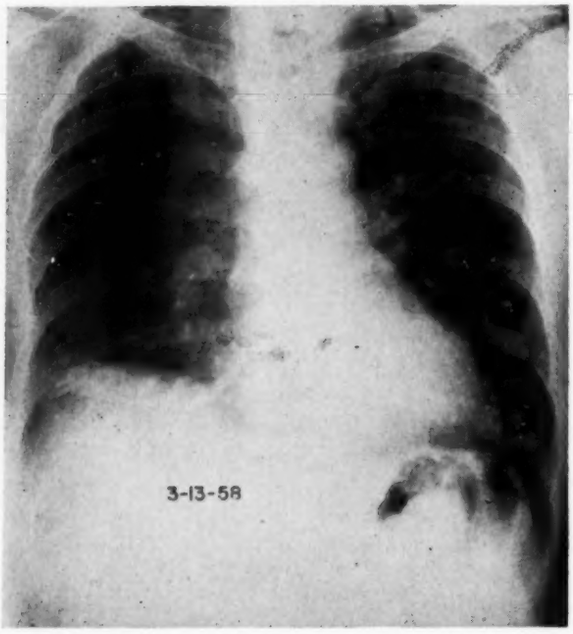

FIG. 4. Roentgenogram of the chest of patient (Case I) showing resolution of the previous abnormalities after corticosteroid therapy.

FIG. 5. Roentgenogram of the chest of patient (Case II) showing diffuse lacelike infiltrates throughout both lung fields.

return of pulmonary symptoms. In August 1959, a right hemiparesis developed and the patient died two months later. Autopsy was not performed.

CASE II. M. M. (New England Center Hospital No. 121–751), a sixty-six year old female teacher, was found to have the blood and bone marrow features of chronic granulocytic leukemia in August 1958. The initial blood counts were: hemoglobin 12.5 gm. per cent, hematocrit 42 volumes per cent, red blood cells 4.65 million per cu. mm., platelet count 680,000 per cu. mm., reticulocytes 7.1 per cent, white blood cells 110,000 per cu. mm. with 16 per cent polymorphonuclear leukocytes, 22 per cent band forms, 3 per cent lymphocytes, 3 per cent eosinophils, 12 per cent basophils, 17 per cent myelocytes, 25 per cent metamyelocytes and 2 per cent blast forms. Treatment with busulfan was begun with an initial dose of 8 mg. daily; eventually a maintenance dose of 2 to 4 mg. per day was achieved. The clinical and hematologic responses to this treatment were satisfactory and the patient was able to resume her usual activities. In September 1959, thirteen months later, she complained of marked weakness and weight loss which could not be accounted for by her hematologic status. The patient had also noticed exertional dyspnea during the preceding year, recently more marked. Because of these symptoms she was admitted to the hospital. On physical examination the patient seemed chronically ill and cachectic. The blood pressure was 100/60 mm. Hg, the pulse rate was 120 per minute and the oral temperature was 99°F. A generalized brownish hyperpigmentation of the skin was present, most marked on the abdomen and extremities. The nipples were somewhat darker than normal. There was no abnormal pigmentation of the mucous membranes. There was neither cyanosis nor clubbing of the fingers. Dry, sharp crackling rales were heard over both lung fields. No hepatosplenomegaly or lymphadenopathy was present. The laboratory data were: hemoglobin 11.2 gm. per cent, hematocrit 39 volumes per cent, red blood cells 3.66 million per cu. mm., platelets, 1.5 million per cu. mm., white blood cells 8,450 per cu. mm. with 70 per cent polymorphonuclear leukocytes, 8 per cent lymphocytes, 2 per cent monocytes, 8 per cent basophils, 5 per cent myelocytes, 4 per cent metamyelocytes, 1 per cent progranulocytes and 2 per cent blast forms. The erythrocyte sedimentation rate was 45 mm. per hour. A biopsy specimen of the bone marrow was hyperplastic with an over-all pattern of chronic granulocytic leukemia. No myelofibrosis was present. The blood urea nitrogen, serum proteins, bilirubin, sodium, potassium, chloride, carbon dioxide content and fasting blood sugar were normal. Cultures of the sputum, blood and urine yielded no pathogens. The tuberculin test had negative results. A study of urinary 17-ketosteroid and 17-hydroxycorticoids before and after ACTH stimulation did not substantiate a definite diagnosis of Addison's disease. The patient was seen by Dr. Kenneth Byrd, as consultant, who made a diagnosis of Hamman-Rich syndrome.

Roentgenograms of the chest showed a diffuse, fine lacelike infiltrate throughout both lung fields. (Fig. 5.) (A roentgenogram of the chest taken in 1957 had shown normal findings.) Pulmonary function studies performed by Dr. Leon Cander revealed

"alveolar hyperventilation with normal arterial oxygen saturation and reduced carbon dioxide content, mild bronchial obstruction, reduced static lung compliance and markedly reduced pulmonary diffusing capacity. The distribution of alveolar gases was within normal limits and the vital capacity was reduced." These findings were deemed compatible with the syndrome of alveolar-capillary block.

During these diagnostic studies fever developed, with temperatures varying between 101°F. to 102°F. rectally. No definite cause for the fever could be found. Because of the abnormal roentgenogram of the chest and pulmonary function studies a lung biopsy was performed. The tissue showed a chronic inflammatory reaction with predominantly interstitial fibrosis diffusely distributed throughout the lung. No granulomas were seen. Many of the septal and alveolar cells were enlarged, with an occasional multinucleated form. The over-all pattern was that of chronic interstitial pneumonitis with fibrosis. No evidence of leukemia or vasculitis was found. (Fig. 6.) Busulfan therapy was discontinued and treatment with prednisone, 100 mg. per day, was initiated. There was prompt defervescence and the patient improved symptomatically. When seen two months later, in December 1959, all pulmonary symptoms had disappeared, but the weakness persisted, and a repeat roentgenogram of the chest showed persistence of the pulmonary infiltrates. In January 1960, pulmonary edema suddenly developed and the patient died at home. No autopsy was performed.

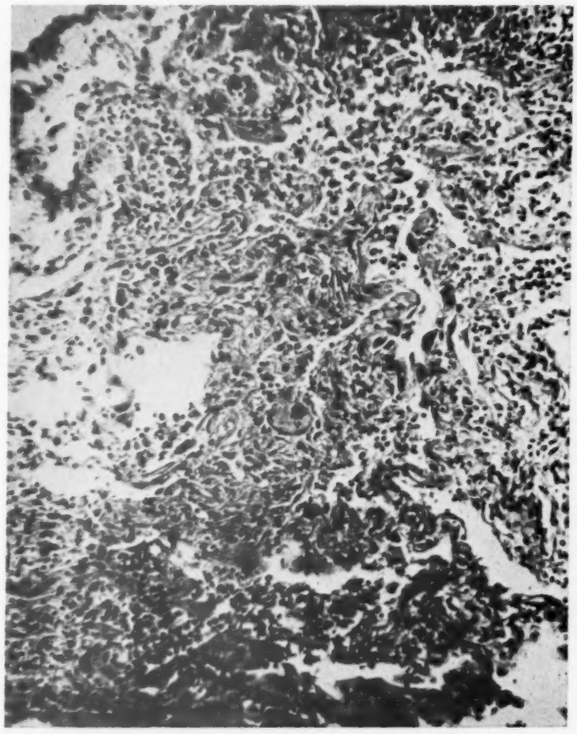

FIG. 6. Photomicrograph of a biopsy specimen of the lung in Case II. Diffuse interstitial fibrosis with a chronic inflammatory reaction can be seen, × 100.

COMMENTS

The two patients herein described showed the characteristic features of chronic granulocytic leukemia. Busulfan therapy was begun promptly, and in both cases excellent responses occurred. The hepatosplenomegaly and leukocytosis disappeared in each case, as expected, and both patients were restored to a state of apparent good health. No gastrointestinal, myelotoxic or other reactions occurred. Nevertheless, within one year after the initiation of busulfan therapy a serious reaction developed in each patient which could not be related to the hematologic disorder. In each case the symptomatology was referable to the lungs, and included dyspnea, fever, weakness and weight loss. One of the patients (Case I) also complained of a dry, hacking cough. The important physical findings were confined to the lungs, where dry crepitant rales were heard. In both patients the leukemic state, as indicated by hematologic studies, was in remission. The erythrocyte sedimentation rate was elevated in each case. Pulmonary function studies were performed in one patient (Case II) and showed the pattern of alveolar-capillary block.

In each case the roentgenograms of the chest revealed remarkable changes following busulfan therapy. These consisted of diffuse, bilateral infiltrates which had the appearance of an inflammatory process. Biopsy specimens of the lung showed a similar picture, consisting of diffuse interstitial fibrosis. One patient (Case I), also had chronic proliferative vasculitis. Steroid therapy in high dosage produced rapid resolution of symptoms and signs. In this patient roentgenograms of the chest reverted to normal.

The development of this pulmonary syndrome during busulfan therapy is strongly suggestive of a hypersensitivity reaction to the drug. No other drugs were taken by these patients before the onset of this complication. Pulmonary fibrosis is not a feature of chronic granulocytic leukemia. Leukemic infiltration of the lung [*4*] is uncommon and is usually seen in acute leukemia or in chronic lymphocytic leukemia [*5*]. The roentgenogram of the chest may show no lesions or miliary or nodular infiltrates may be seen. In a case described by Nathan and Sanders [*6*], the alveolar-capillary block syndrome was produced by interalveolar

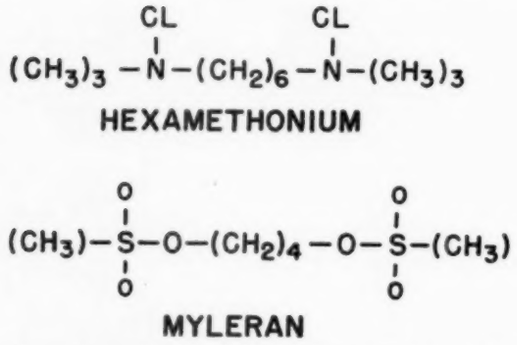

FIG. 7. Chemical structures of busulfan (Myleran) and hexamethonium.

leukemic infiltrates. The diagnosis of leukemic involvement of the lung is usually made at autopsy, where invasion of the alveolar septums, focal collections of leukemic cells around small bronchioles and blood vessels, or subpleural infiltrates may be found. None of these changes were found in the biopsy specimens of the lung obtained from the two patients reported on in this paper.

Pulmonary fibrosis with alveolar-capillary block may be seen following extensive radiation of the lungs [*7*]. Although our patients did not receive x-ray therapy, they were treated for a prolonged period with an alkylating agent which has "radiomimetic" properties. In the experimental animal treated for protracted periods with busulfan, cataracts have occasionally resulted, but in no instance has fibrosis of the lung been observed [*8*]. Adrenal steroid therapy has been used in the treatment of radiation fibrosis of the lung, invariably with failure to reverse the course of the pulmonary lesions, although symptomatic relief may occur [*9*]. In contrast, one of our patients showed striking resolution of the pulmonary lesions after treatment with prednisone. Although the radiomimetic action of busulfan may account for the pulmonary fibrosis in our patients, we believe that this possibility is unlikely in view of the absence of other evidence of radiation damage and their response to prednisone.

A syndrome of pulmonary disease has been well documented in hypertensive patients treated with hexamethonium. It was first reported in 1953 by Morrow, Schroeder and Perry [*10*] who described five patients with diffuse interstitial fibrosis of the lungs following therapy with the drug. Following their report, others of similar cases followed [*11,12*]. The general features of the hexamethonium-induced pulmonary syndrome may be summarized as follows: the onset of the syndrome occurs from one to twelve months after the initiation of hexamethonium therapy; the symptoms include tachypnea, fever and dyspnea; cyanosis and cough are uncommon. The roentgenographic findings consist of bilateral, mottled or linear densities which may simulate pulmonary tuberculosis. Histologic examination of the lung discloses pulmonary fibrosis [*10–12*], fibrinous pneumonitis [*13*], or organized fibrinous pulmonary edema [*14*]. Pathologic findings similar to those of our patients, except for the proliferative endarteritis in Case 1, were described by Morrow et al. [*10*], Robillard et al. [*11*] and Petersen et al. [*12*]. The microscopic findings in two of these reports [*10,11*] were identical with those described by Hamman and Rich [*15*]. A high mortality rate was associated with the development of this syndrome. In two of the reported cases steroid therapy was ineffective. The cause of the pulmonary fibrosis which develops during hexamethonium therapy is unknown. Several explanations have been offered: it may be the result of (1) prolonged pulmonary edema during attacks of congestive heart failure, (2) pooling of blood in the pulmonary circulation, (3) an azotemic-like effect, or (4) it may represent an acquired "collagen" disease.

The clinical, radiologic and histologic features of our cases are strikingly similar to those seen in patients in whom the syndrome develops following hexamethonium therapy. This would suggest a common etiologic factor in these two groups of patients. When the chemical structures of busulfan and hexamethonium are compared, a certain similarity is apparent. (Fig. 7.) Both are straight chain compounds, symmetrically methylated. While the terminal methyl groups in hexamethonium are linked to the central chain by nitrogen atoms, in busulfan this linkage is through sulfone groups. It is conceivable that in the sensitive person this general class of compound could elicit a pulmonary fibrotic reaction. Failure to develop a severe attack of interstitial pulmonary fibrosis when re-exposed to busulfan is not unexpected. Thus, re-exposure to hexamethonium does not necessarily induce a second episode of interstitial pulmonary fibrosis; furthermore, patients with chlorpromazine jaundice may not develop a second episode on re-exposure to that drug. These curious differences in behavior of supposed hypersensitivity reactions to drugs on

re-exposure to the inciting agent remain unexplained.

Whereas chronic lymphocytic leukemia is not uncommonly associated with immunologic disturbances, such an association is very rare in chronic granulocytic leukemia. The usual immunologic complication seen in chronic lymphocytic leukemia is autoimmune hemolytic anemia [*16*], although idiopathic thrombocytopenic purpura [*17*] and vasculitis [*18*] have been observed. This difference in behavior can be accounted for by the difference in the proliferating cell types. Chronic lymphocytic leukemia is characterized by massive production of lymphocytes, immunologically competent cells, while the granulocyte of chronic granulocytic leukemia plays no discernible role in antibody formation. This would strongly suggest that an immunologic reaction occurring during the course of chronic granulocytic leukemia is not due to the underlying disease but to some extraneous factor resulting in an abnormal immune response.

SUMMARY

The development of diffuse interstitial pulmonary fibrosis was observed in two patients with chronic granulocytic leukemia treated with busulfan. A hypersensitivity to busulfan, similar to that seen after hexamethonium therapy, is considered the most likely pathogenic mechanism. Treatment with large doses of prednisone resulted in striking resolution of the pulmonary symptoms and signs.

Acknowledgment: We are indebted to Dr. Robert McCombs who helped in the management of Case I.

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Retinopathy Associated with Chloroquine Phosphate Therapy*

R. D. Richards, M.D. *and* W. R. Wilson, M.D.
Iowa City, Iowa

Chloroquine phosphate (Aralen®) was first introduced as an antimalarial drug but in the past few years it has been used in the treatment of amebiasis, disseminated and discoid lupus erythematosus, and rheumatoid arthritis. Soon after its introduction transitory visual symptoms were noted by many patients [*1*]. The reason for these visual difficulties was not determined. More serious toxic effects were reported in 1958 when corneal deposits were observed in some patients who had been taking large doses of chloroquine phosphate for four to eight weeks [*2–4*]. The symptoms associated with the corneal changes were blurring of vision and halos around lights. The symptoms and corneal deposits sometimes improved markedly, sometimes disappeared with discontinuance of the drug.

Nevertheless, visual disturbances have not been generally regarded as a problem in the long term treatment of lupus erythematosus and rheumatoid arthritis with chloroquine phosphate. Bagnall [*5*], in a four year study of the use of chloroquine phosphate in rheumatoid arthritis, did not report any significant ocular symptoms. Young [*6*], describing the results of chloroquine phosphate therapy for eighteen to thirty-six months in fifty consecutive patients with rheumatoid arthritis, stated that toxic reactions were infrequent, mild and easily reversible. In a report on rheumatic diseases, however, the Committee of the American Rheumatism Association stated that toxic reactions to the administration of chloroquine, such as blurring of vision, developed in some patients and occasionally necessitated discontinuation of the drug [*7*].

Recently Hobbs, Sorsby and Freedman [*8*] reported a serious complication of chloroquine phosphate therapy. In three patients reduction of the visual field and impaired central vision developed. Ophthalmoscopic examination revealed marked narrowing of the retinal arteries and abnormalities of the macula, consisting of edema or pigmentation. All three patients had been treated with large doses of chloroquine phosphate for approximately three years for either discoid lupus erythematosus or rheumatoid arthritis. The visual changes did not regress after the administration of chloroquine phosphate was discontinued.

We have seen a patient who showed similar changes while taking chloroquine phosphate for an extended period of time.

CASE REPORT

S. D. H., a white woman forty-two years of age, with cerebral palsy, had rheumatoid arthritis in 1949. She was treated with cortisone for five and a half years. During this therapy osteoporosis developed followed by spontaneous vertebral fractures. The cortisone was discontinued and chloroquine phosphate (Aralen, 500 mg. per day) was started in January 1958. Complete relief of joint symptoms was obtained after several weeks of treatment, and treatment was continued. Ocular examination in May 1959 was within normal limits, with vision correctable to 20/20 in each eye. In October 1959 she noted the onset of visual difficulty. Central visual acuity was good but she had difficulty seeing simultaneously several objects spread out on a table. In February 1960 she noted blurring of central vision.

She was seen at University Hospitals on May 9, 1960. Vision was correctable only to 20/40 in each eye. Both corneas showed superficial infiltrates characteristic of the changes associated with chloroquine phosphate therapy. Visual fields showed loss of the entire upper field in each eye and constriction of the remaining lower island of field. (Fig. 1.) Intraocular tension was normal. The ophthalmoscopic examination revealed interesting changes. (Fig. 2.) Generalized narrowing of the retinal arteries was seen. The inferior arteries were even more markedly constricted than the superior arteries. No focal constrictions were

* From the Departments of Ophthalmology and Internal Medicine, State University of Iowa, Iowa City, Iowa.

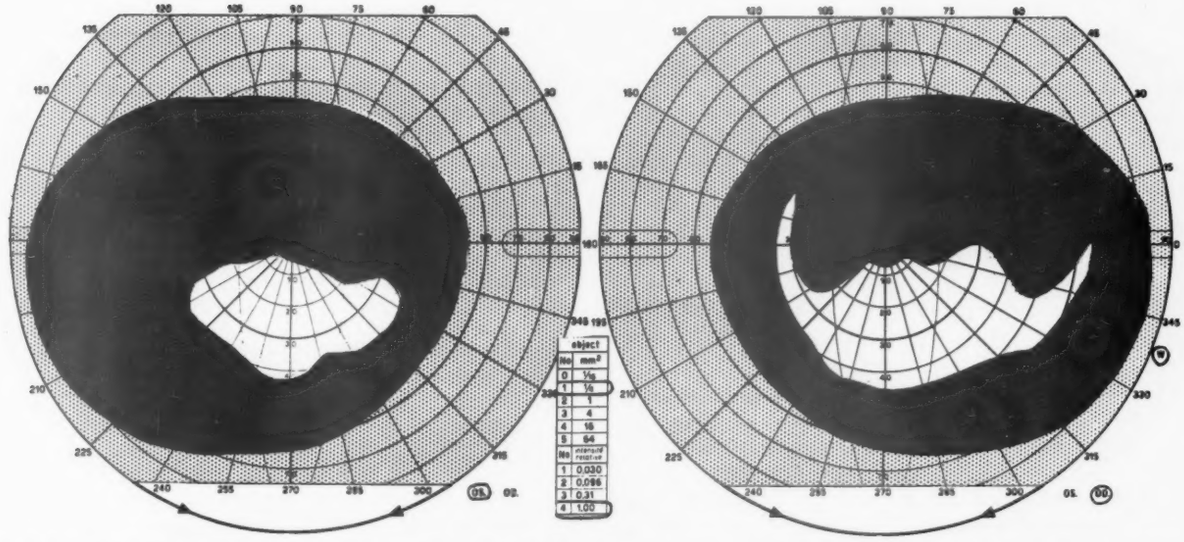

FIG. 1. The visual field charts were obtained on the Goldmann perimeter. The dark area on each chart indicates a normal field and the white area shows the remaining visual field of the patient. The field loss is greater in the left eye.

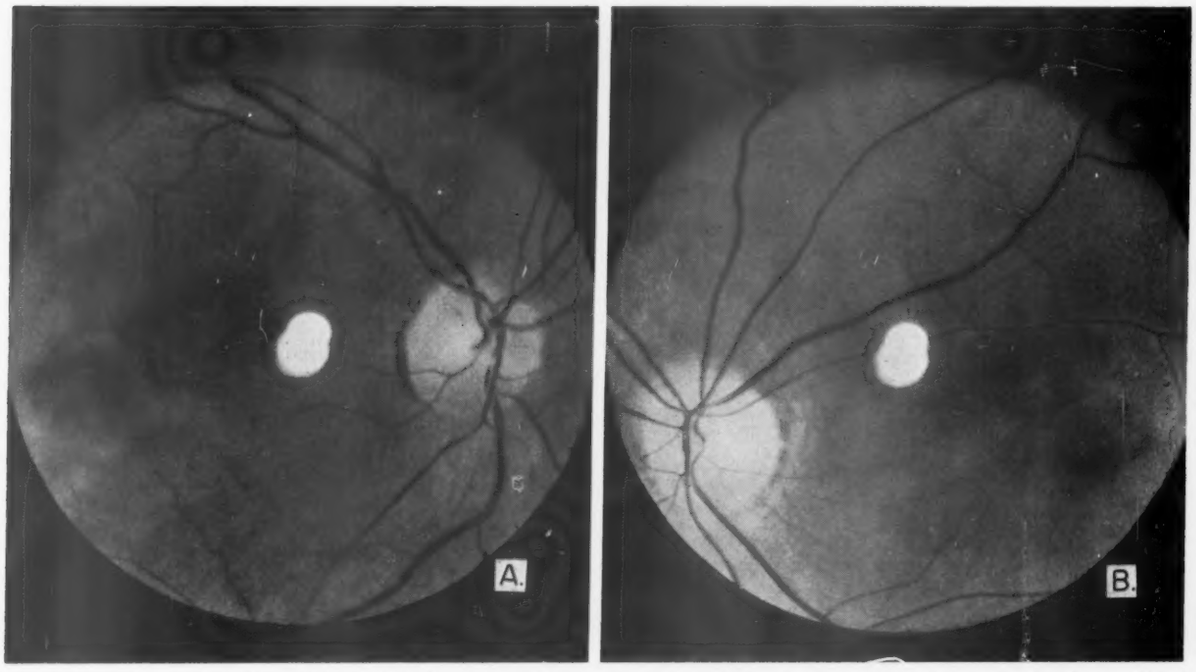

FIG. 2. A, right eye. B, left eye. Edema is indicated by the grey area around the darker center of the macula. Generalized narrowing of the retinal arteries is also present.

seen. Arteriosclerotic changes (increased light reflex, perivascular sheathing, changes at the arteriovenous crossings) were not present. The veins were normal. The maculas were edematous and elevated, and had an opaque, greyish appearance. When examined with a slit lamp, the fovea was slightly depressed. No cyst was seen. The discs showed only slight temporal pallor. No hemorrhages, exudates or abnormal pigmentary changes were present.

Functional tests of the retinas by means of dark adaptation and electroretinographic studies were performed. Rod adaptation was delayed and the threshold after forty minutes in complete darkness was about one and a half log units above the normal. No responses were obtained with white or colored light stimuli in the electroretinogram. These findings are indicative of severe retinal damage, probably more severe in the outer layers of the retina.

Physical examination revealed no signs of generalized vascular disease. The blood pressure was 110/60 mm. Hg. Cardiac examination was within normal limits. She had kyphosis of the chest, with a marked scoliosis. The lower thoracic vertebrae were prominent. The proximal interphalangeal joints of the hands showed the characteristic spindle-shaped deformities of rheumatoid arthritis. No signs of active inflammatory disease of the joints were found.

The hemoglobin was 14.2 gm. per 100 ml., the red cell count was 4,440,000 per cu. mm., the white cell count was 4,800 per cu. mm., and the differential was normal. The results of urinalysis were normal. The erythrocyte sedimentation rate was 12 mm. per hour (Westergren method). The serum total proteins were 6.9 gm. per cent with 4.6 gm. per cent albumin and 2.3 gm. per cent globulin. The serum total cholesterol was 189 mg. per cent. The blood urea nitrogen was 14 mg. per cent and the serum creatinine was 1.2 mg. per cent. The lupus erythematosus cell preparation was negative. Results of the serological test for syphilis (Kolmer) were negative. Skull and orbital roentgenograms revealed no abnormalities. The roentgenograms of the chest revealed no abnormalities other than the kyphosis and scoliosis.

Chloroquine phosphate therapy was discontinued and six weeks later the patient was re-examined. Visual acuity and the visual fields were unchanged. The corneal deposits were still present but had regressed. Ophthalmoscopic examination revealed no change in the fundus. Physical examination was also unchanged. There had been no recurrence of the joint symptoms.

COMMENTS

Drugs such as quinine, aspidium, salicylates and ergot are known to cause visual changes [*9*]. These are characterized by peripheral constriction of visual fields, the ophthalmoscopic examination usually showing narrowing of the retinal arteries. Macular edema may appear as an early sign, followed by optic atrophy. It would seem reasonable to include chloroquine phosphate in this group on the basis of the retinal changes observed.

The pathogenesis of these changes is not known. These drugs may act directly on the nerve elements but the marked vasoconstriction seems to be an important part of the picture.

Other conditions which may show somewhat similar changes should be considered in the differential diagnosis. Central serous choroidosis usually affects young men and presents a clinical picture of edema of the macula. The condition is usually unilateral, however, and the retinal arteries are not narrowed. Also, hemorrhages around the macula are sometimes present. Braley and Hamilton [*10*] reported on patients with central serous choroidosis associated with amebiasis, but the characteristic finding was a cyst in the macula. Woods and Wahlen [*11*] reported retinal findings associated with a positive histoplasmin reaction. These consisted of a small subretinal cyst in the macula with surrounding edema, often hemorrhages, and peripheral lesions consisting of focal spots of atrophic chorioretinitis. Toxoplasmosis often affects the macula but usually is associated with very marked proliferation of pigment as well as other areas of chorioretinitis in the periphery. Disciform degeneration of the macula is characterized by hemorrhages followed by proliferation of connective tissue between the retina and choroid. Retinitis pigmentosa is characterized by marked narrowing of the retinal arteries, a waxy disc, and pigmentary proliferative changes in the periphery.

Two other reports of visual changes after the administration of chloroquine phosphate therapy suggest a similar retinopathy but there are not enough sufficient details to be sure. Sternberg and Laden [*12*] reported bilateral macular degeneration in a thirty-two year old woman after being treated for discoid lupus erythematosus for four and a half years with chloroquine phosphate. A description of the retinal lesions and the visual field changes was not given. Goldman and Preston [*13*] reported that in two patients retinal changes developed after their treatment with the administration of large doses of chloroquine phosphate for lupus erythematosus. The ophthalmoscopic findings were not described, but one patient was reported to have had constricted visual fields. At the postmortem examination the eyes were removed and examined histologically, but no cause for the visual change was found.

It is possible that additional patients have retinal changes caused by long term chloroquine phosphate therapy but these may have been overlooked since the relationship of retinopathy to chloroquine phosphate has been reported so recently.

SUMMARY

Persistent retinal changes with loss of vision have been reported after long term chloroquine phosphate therapy.

An additional patient with similar changes is presented herein. After two and a half years of chloroquine phosphate therapy for rheumatoid

arthritis, our patient had visual field loss, decreased central vision, corneal deposits and retinopathy consisting of marked arterial constriction and edema of the macula.

Since the visual loss is apparently permanent, patients on long term chloroquine phosphate therapy should have periodic ocular examinations with special emphasis on slit lamp, ophthalmoscopic and visual field examinations.

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Thyroid Autoantibodies and a Biologic False-Positive Reaction to the Test for Syphilis*

HERBERT A. SELENKOW, M.D., MARTIN J. CLINE, M.D., HUGH FUDENBERG, M.D.
and MARCUS S. BROOKE, PH.D.

Boston, Massachusetts

A BIOLOGIC false-positive serologic test result for syphilis has been reported in disorders of diverse etiology. Prominent among these are infectious disorders such as leprosy, malaria, relapsing fever and various viral diseases, and non-infectious systemic states including connective tissue-vascular diseases, hepatitis and acquired hemolytic anemias [*1,2*]. One factor common to these is the frequent occurrence of elevated levels of serum globulins. To our knowledge, there has been no previous published report of a biologic false-positive reaction to the serologic test for syphilis in chronic lymphoid thyroiditis (Hashimoto's struma). Circulating autoantibodies to thyroglobulin or to cellular constituents of the thyroid gland have been demonstrated in this disorder [*3–6*] in association with elevated levels of serum gammaglobulin [*7*].

The patient with chronic lymphoid thyroiditis described in this report has elevated serum levels of gammaglobulin, high titers of circulating antibodies to thyroglobulin and a persistent biologic false-positive reaction to the serologic test for syphilis. A detailed study of this patient's serum was undertaken to characterize the circulating thyroid antibodies and, if possible, differentiate them from Wassermann antibody.†

CASE REPORT

This fifty year old Canadian housewife was first admitted to the Peter Bent Brigham Hospital on May 27, 1957, for evaluation of chronic fatigue. She had had a goiter since the age of thirteen years but had remained asymptomatic until the present illness. At the age of twenty-two she had mild preeclampsia with her first pregnancy. At the age of thirty-four she was thought to have a "toxic" goiter; and at thirty-seven she underwent her first subtotal thyroidectomy for symptoms suggestive of mild hyperthyroidism. Several months postoperatively she experienced transient generalized swelling of her face, abdomen and extremities which was presumed to be due to hypothyroidism, but no therapy was instituted. At the age of forty she had an hemoptysis; and a chest roentgenogram was reported to show tuberculosis. The patient was hospitalized in a sanitarium for three months where she had two subsequent hemoptyses, but no acid-fast organisms were found. Subsequent follow-up chest roentgenograms have not demonstrated evidence of any active pulmonary process.

During her stay in the sanitarium she had a second subtotal thyroidectomy for recurrent goiter. The diagnosis of "hyperplastic nodular goiter" was reported on histologic examination of the excised thyroid tissue.

Approximately eight years prior to the present admission, at age forty-two, hypertension was noted for the first time with systolic pressures as high as 240 mm. Hg. She has subsequently received hydralazine, reserpine and several other antihypertensive medications. No symptoms of hypertension other than mild exertional dyspnea have been noted.

Six months prior to admission the patient's condition apparently changed abruptly. She became progressively more lethargic and more easily fatigued. She experienced intolerance to cold, dry skin, generalized puffiness, deepening of her voice, loss of libido and a weight gain of approximately 20 pounds.

On admission physical examination revealed a somewhat large-framed, moderately obese, lethargic, pasty-skinned woman. The blood pressure was 215/140 mm. Hg, pulse 40 and regular. There was a well healed thyroidectomy scar. The thyroid gland was approximately five times enlarged, quite lobu-

† As used in this paper, the term "Wassermann antibody" designates that substance in serums which reacts with antigens (exclusive of the treponemal antigens) commonly used in serologic tests for syphilis.

* From the Department of Medicine and the Department of Bacteriology and Immunology, Harvard Medical School, and the Peter Bent Brigham Hospital, Boston, Massachusetts. This study was supported in part by the William F. Milton Fund and in part by the Thyroid Research Laboratory, Peter Bent Brigham Hospital.

lated, and had a rubbery consistency. The patient's speech was slow and somewhat slurred. She appeared depressed. Her skin was dry, cool and thickened. No proptosis or pretibial myxedema was present. The cardiac silhouette was within the upper limits of normal size to percussion. There were no heart murmurs. The liver was palpable at the costal margin. The remainder of the physical examination was within normal limits.

Laboratory studies revealed a hematocrit of 47 per cent; sedimentation rate, 39 mm./hour (Wintrobe); platelet count, 166,000 per cu. mm.; white blood cells, 7,000 per cu. mm.; normal differential count; blood group AB, Rh positive. Urinalysis disclosed no abnormalities. Serum chemistries included a blood urea nitrogen of 10 mg. per cent; cholesterol, 466, 430 and 387 mg. per cent; fasting blood sugar, 70 mg. per cent; phosphorus, 1.1 mM. per L.; alkaline phosphatase, 3.8 Bodansky units; bilirubin, 0.66 mg. per cent. There was normal bromosulphalein excretion. The results of the phenolsulfonphthalein test showed 65 per cent excretion in two hours. Urinary catecholamines were less than 100 μg. per twenty-four hour specimen (normal). Examination of the cerebrospinal fluid was within normal limits except for a protein of 78 mg. per cent. Results of skin testing with first strength P.P.D. were negative at forty-eight hours. Roentgenographic examination of the chest revealed the heart to be slightly enlarged in the transverse diameter, with a left ventricular configuration. Roentgenograms of the skull revealed a normal sella turcica. Intravenous pyelography disclosed no abnormalities. Electrocardiogram showed nonspecific lowering of T waves and normal voltage. Red blood cell uptake of radioactive triiodothyronine [8] was 15 per cent (normal). Serum protein-bound iodine was 9.2 and 7.2 μg. per cent. After replacement therapy with 100 μg. of triiodothyronine, the serum protein-bound iodine fell to 2.6 μg. per cent and the serum butanol-extractable iodine was found to be 2.4 μg. per cent. Twenty-four hour radioactive iodine uptakes were 39 and 34 per cent on two successive occasions. The basal metabolic rate was minus 13 per cent and minus 12 per cent. The serum electrophoretic pattern was normal except for increased gammaglobulin (1.53 gm. per 100 ml.).

TABLE I
SEROLOGIC TESTS FOR SYPHILIS

1952	Kahn	Negative
	Standard Kahn	Doubtful (±)
	Kolmer-Wassermann	Doubtful (±)
	Kahn	Positive
1957	Hinton	Positive 1:4
	T.P.C.F.	Negative
	C.S.F.	Negative
1958	T.P.C.F.	Negative (on 2 occasions)
	T.P.I.	Negative
	Hinton	Positive 1:8
	Kolmer-Wasserman	Positive

NOTE: T.P.C.F. = Treponema pallidum complement fixation (test).
C.S.F. = Cerebrospinal fluid.
T.P.I. = Treponema pallidum immobilization (test).

The results of serum flocculation and complement fixation tests for syphilis and the results of serologic tests for systemic lupus erythematosus and rheumatoid factors appear in Tables I and II. The titers for the tanned erythrocyte agglutination and the results of the complement-fixation tests for thyroid antibody appear in Tables III and IV and in Figure 1.

A large hyperplastic nodule was excised from the right lobe of the thyroid. Microscopic examination revealed increased interstitial fibrous tissue with interlacing fibrous bands separating groups of thyroid follicles. The interstitial tissue contained numerous plasma cells and lymphocytes with a few lymphoid follicles with germinal centers. The acinar cells of many of the follicles were tall. The final pathologic diagnosis was chronic thyroiditis.

Despite laboratory evidence indicating euthyroidism, the patient was treated with thyroid substitution therapy in order to suppress any further growth of her

TABLE II
SERUM FACTORS

Cephalin flocculation	4+
Thymol turbidity	82, 80, 61 units (normal 0–40 units)
C-reactive protein	0
Serum mucoproteins	3.0 mg. % (normal 2.0–2.5 mg. %)
S.L.E. cell determination (Snapper and Hargreaves)	Negative (2 determinations)
Fluorescent S.L.E. reaction	Negative
Complement-fixation test for S.L.E.	Negative (DNA and muscle protein)
Rheumatoid factors	Negative
Latex fixation	
Sheep red cells	
Coated human red cells	
Heated gammaglobulin precipitation test	

TABLE III
SERUM THYROID ANTIBODIES (HEMAGGLUTINATION METHOD)

January 1958	Thyroid extract	1:1,300,000
	Thyroglobulin	1:100,000
May 1958	Thyroid extract	1:1,300,000
	Thyroglobulin	1:81,000
November 1958	Thyroid extract	1:5,200,000

No antibodies to saline extracts of normal human lung, kidney or liver were detected by hemagglutination assay.

Results of complement fixation tests were negative against saline extracts of normal human thyroid, kidney, liver or lung as antigen.

TABLE IV
DENSITY GRADIENT ULTRACENTRIFUGATION

Fraction		Hemagglutination Titer
1	Albumin	1:320
2	7-S	1:5120
3	10 to 12-S	1:40
4	Intermediate Zone	1:20
5	19-S	1:20

goiter. Follow-up examinations on several subsequent occasions revealed decrease in the size of her thyroid with improvement in general well-being and appearance.

RESULTS OF IMMUNOLOGIC STUDIES

Serologic Tests for Syphilis. Over a six year period the patient had had repeatedly positive reactions to the Kahn, Kolmer-Wassermann and Hinton serologic tests for syphilis. However, results of the treponema pallidum immobilization [*9*] and the Reiter protein complement fixation [*10*] tests have been consistently negative. (Table I.)

Hemagglutination, Complement Fixation and Precipitation Reactions (*Table* III). Serums from this patient, tested by the tanned erythrocyte hemagglutination technic [*11*], had a high titer with saline extracts of normal human thyroid gland and with human thyroglobulin prepared according to the method of Derrien and associates [*12*]. By the same technic, these serums failed to react with saline extracts of human liver, lung or kidney. The serums did not fix complement when tested against extracts of normal human thyroid as well as kidney, liver or lung. Saline extracts of normal human thyroid gland (protein concentration 7 mg. per ml) in dilutions up to 1:1,000 produced visible precipitation when added to the patient's undiluted serum. Controls with normal human serum albumin were negative.

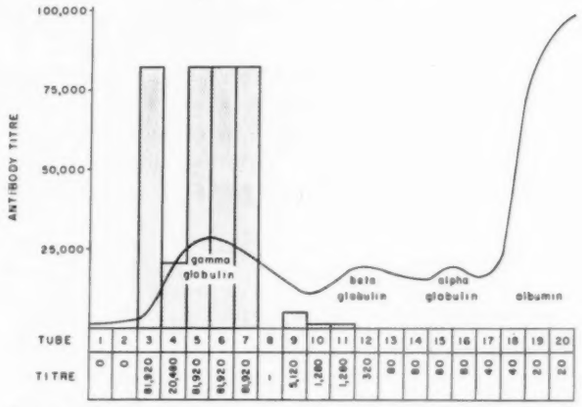

FIG. 1. Starch block electrophoretic separation of serum. Hemagglutination assay using thyroid extract was performed against each of the twenty fractions. The pattern designated by the black line is the serum electrophoretic pattern superimposed upon the results of the hemagglutination assay.

Zone Electrophoresis. Zone electrophoresis was performed on a starch supporting medium using barbital buffer at pH 8.6 ($\mu = 0.05$) [*13*]. Protein was eluted from ½ inch segments by displacement filtration, and its concentration estimated by a modified Folin tyrosine method [*14*]. The hemagglutination titer of each fraction is presented in Figure 1. By this technic, the largest portion of the thyroid antibodies was in fractions 3 to 7, corresponding to the major peak of the gammaglobulins. Efforts to localize the Wassermann antibody were unsuccessful because the fractions obtained by zone electrophoresis were too dilute to permit a positive result with the Hinton or the Kolmer-Wassermann tests.

Density Gradient Ultracentrifugation. Five fractions of the plasma proteins were obtained by density gradient ultracentrifugation [*15*]. The highest titer of thyroid antibodies was found in fraction 2 which corresponds roughly to the 7-S fraction. No significant thyroid antibody was found in the 10-S to 12-S or the 19-S fractions. (Table IV.) The activity in fraction 1 (albumin) represents small amounts of the 7-S gammaglobulin which is rarely completely separable from albumin by this method.

Passive Cutaneous Anaphylaxis Reaction. Passive cutaneous anaphylaxis studies were performed in guinea pigs using ultracentrifugation fractions of the patient's serum and normal thyroid extract as antigen [*16*]. The 7-S fraction gave a positive test result in dilutions up to 1:500. The

other four fractions (Table IV) gave negative passive cutaneous anaphylaxis reactions.

Differentiation of Thyroid Antibody from Wassermann Antibody. Differentiation of thyroid antibody from Wassermann antibody was accomplished by absorption of the patient's serum with washed, minced human thyroid gland. Following absorption the serum was found to be emptied of its titer against thyroid antigen by the hemagglutination assay. The Kolmer-Wassermann complement fixation reaction of this absorbed serum was still strongly positive.

COMMENTS

The concurrence of a biologic false-positive reaction to the serologic test for syphilis and of circulating antibodies to thyroid antigens may be fortuitous or may represent a relationship between the two immunologic systems.

Autoimmune processes have been implicated in chronic lymphoid thyroiditis and other thyroidal disorders. In these conditions antibodies directed against extracts of thyroid gland have been demonstrated. There is evidence that more than one thyroidal antigen is involved in this immunologic system. Serums from the majority of patients with lymphoid thyroiditis give hemagglutination and precipitin reactions with saline extracts of normal human thyroid but not against extracts of other organs. Relatively few serums give positive complement fixation reactions with normal human thyroid antigen, but a significant number fix complement when tested against extracts obtained from thyrotoxic glands. It has been suggested that the complement-fixing antibodies are directed against the microsomal constituents of thyroid cells which are abundant in the hyperplastic glands of thyrotoxic patients. However, a small number of serums with complement-fixing antibodies against thyroid antigen fix complement with extracts of brain, liver, kidney or adrenal gland [*4*]. Thus in some instances these antibodies may not be entirely specific for thyroidal antigen but may react with antigens common to several tissues. Precipitating or hemagglutinating antibodies, on the other hand, appear to react specifically with thyroglobulin.

In the patient herein described the major portion of the thyroidal antibody was localized in the gammaglobulin fraction when the serum was fractionated by zone electrophoresis in barbital buffer. With separation of serum protein components by density gradient ultracentrifugation, the peak antibody titer was found in the 7-S fraction and was negligible in the 19-S fraction. Only the 7-S fraction produced a passive cutaneous anaphylaxis reaction in high dilution when tested against thyroid antigen, confirming the presence of thyroid antibody in this fraction.

A biologic false-positive reaction to the serologic test for syphilis is probably not a simple function of elevated serum globulins since numerous systemic disorders associated with hyperglobulinemia fail to exhibit false-positive reactions [*1*]. Some diseases in which false-positive reactions are observed may be considered immunologically responsive. This is particularly true of the infectious disorders. In other conditions, such as disseminated lupus erythematosus, immunologic hyperreactivity or autoreactivity has been postulated, and serum proteins reactive against certain tissue antigens have been demonstrated [*17*]. A false-positive reaction to the test for syphilis has not been previously described in a patient with lymphoid thyroiditis, a condition exhibiting autoantibodies. The most parsimonious hypothesis to explain this association is that the thyroid antibodies are identical with or share reactive groups with Wassermann antibody and are thus responsible for the false-positive test result for syphilis. However, selective absorption of thyroid antibodies from the serum of this patient failed to substantiate this hypothesis. A positive Kolmer-Wassermann reaction for syphilis was obtained with the absorbed serum completely devoid of thyroid antibody. This suggests that the thyroid and Wassermann antibodies are not identical. However, each may be independently related to a hyperimmune state. The possibility exists that certain cases of chronic thyroiditis are examples of an "autoimmune" disorder with abnormal circulating protein constituents directed against multiple tissue antigens. Evidence supporting this concept is afforded by the occasional occurrence of complement-fixing antibodies against several tissues and by the reported finding of lupus erythematosus cells [*18*] and now of a false-positive reaction for syphilis in chronic thyroiditis. In such cases the presence of thyroid autoantibody may be a reflection of a more generalized state of immunologic hyper-reactivity. This situation would correspond to Burnet's [*19*] postulation of the hypermutability of antibody-forming clones which can then react with many body antigens.

SUMMARY

The simultaneous occurrence of antibodies against thyroglobulin and a biologic false-positive reaction to a test for syphilis in a patient with chronic lymphoid thyroiditis is described.

Antibody to thyroglobulin was localized in the 7-S fraction of serum gammaglobulin.

Differentiation of Wassermann antibody from thyroid antibody was achieved by absorption of the serum with minced normal thyroid gland.

The possible implications of the concurrent appearance of these two immunologic conditions is discussed.

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Diffuse Interstitial Leukemic Infiltration of the Lungs Producing the Alveolar-Capillary Block Syndrome*

Report of a Case, with Studies of Pulmonary Function

MYRON E. RESNICK, M.D., RICHARD D. BERKOWITZ, M.D.† *and* THEODORE RODMAN, M.D.
Philadelphia, Pennsylvania

STUDIES of postmortem material indicate that leukemia frequently infiltrates the lung [*1–3*]. The clinical counterpart of such infiltration, however, is not commonly recognized, and a distinct pattern of deranged pulmonary function due to leukemia has rarely been reported [*1,4*]. We have recently studied a patient with acute myelogenous leukemia whose chief complaint throughout most of his illness was dyspnea. Studies of pulmonary function demonstrated the physiologic pattern of an "alveolar-capillary block." Lung tissue examined after death revealed extensive infiltration of the alveolar-capillary interface by leukemic cells, the anticipated morphologic counterpart of the demonstrated pathophysiology.

CASE REPORT

A thirty-seven year old white man (E. W.) was hospitalized at another hospital on December 2, 1958, because of cough, pleuritic pain in the left side of his chest, dyspnea, anorexia and weight loss. He had been in good health until six weeks prior to hospitalization. Physical examination revealed a pale, tachypneic man with many cutaneous petechiae. Coarse rales were heard over both lung fields. The liver was greatly enlarged and slightly tender. The spleen was just palpable. There was generalized moderate lymphadenopathy.

A diagnosis of acute monocytic leukemia was made on the basis of a white blood count of 200,000 per cu. mm. (of which 96 per cent were monocytes) and the appearance of the bone marrow smears. Roentgenographic examination of the chest (Fig. 1) showed only prominence of the interstitial markings. A second chest roentgenogram (Fig. 2) nine days later showed extensive bilateral pulmonary infiltrates, mediastinal lymphadenopathy and probable cardiac enlargement. During the interval between the two examinations there had been deterioration of the patient's condition with no apparent response to treatment for congestive heart failure and pneumonitis. Antileukemic treatment with 300 mg. daily of 6-mercaptopurine was begun on December 5, 1958.

Because of the likelihood that the pulmonary parenchymal changes represented leukemic infiltration, 25 r in air of cobalt radiation was given on two consecutive days over a mid-anterior portal measuring 20 by 20 cm. Examination of the chest (Fig. 3) five days after completion of the cobalt treatment and thirteen days after initiation of the 6-mercaptopurine therapy revealed partial resolution of the pulmonary infiltrates and mediastinal adenopathy but greater cardiac enlargement. The patient experienced complete hematologic remission and was discharged from the hospital on December 28, 1958. He was maintained on 50 mg. of 6-mercaptopurine daily.

Because of an increase in the white blood count to 83,000 per cu. mm., the patient was admitted to the Philadelphia Veterans Administration Hospital on January 21, 1959. Physical examination revealed a tachypneic white man with a tachycardia of 120 per minute. Fine moist rales were heard at the base of both lungs. The heart was slightly enlarged to percussion. The second heart sound was accentuated in the pulmonic area. The venous pressure was 110 mm. of water, and the arm to tongue circulation time thirteen seconds. A tender liver edge was felt 3 fingerbreadths below the right costal margin. The spleen could not be palpated. Small matted lymph nodes were felt in the cervical and axillary regions. The initial white blood count was 78,400 per cu. mm.; hemoglobin was 14.6

* From the Medical Service and Cardiopulmonary Function Laboratory of the Philadelphia Veterans Administration Hospital, Philadelphia, Pennsylvania.
† Present address: Temple University Hospital, Philadelphia, Pennsylvania.

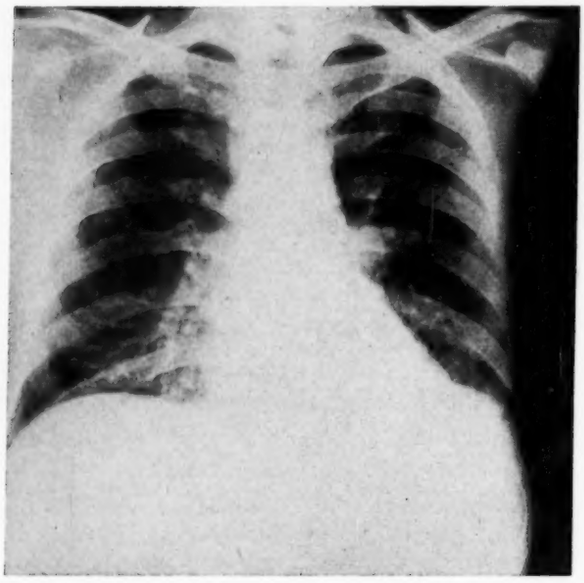


FIG. 1. Posteroanterior roentgenogram of the chest taken on December 2, 1958, which is within normal limits except for prominence of the interstitial markings.

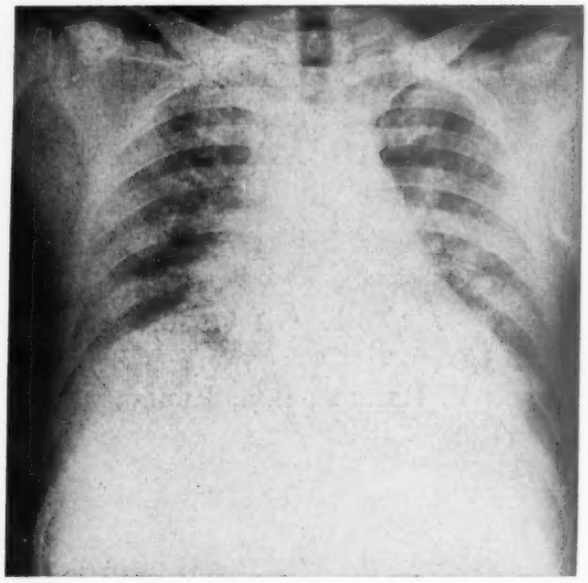


FIG. 2. Posteroanterior roentgenogram of the chest taken on December 11, 1958, showing probable cardiac enlargement, mediastinal and hilar lymphadenopathy, and bilateral pulmonary interstitial infiltrates with areas of confluence.

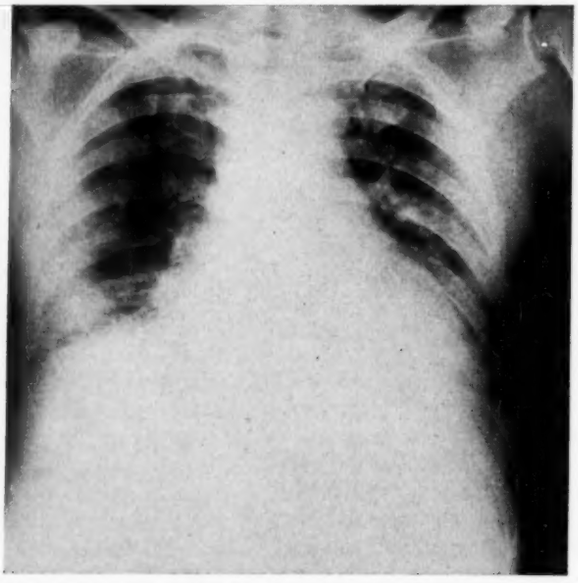


FIG. 3. Posteroanterior roentgenogram of the chest taken on December 18, 1958 (one week after Fig. 2), showing definite cardiac enlargement but less lymphadenopathy and partial resolution of the interstitial process.

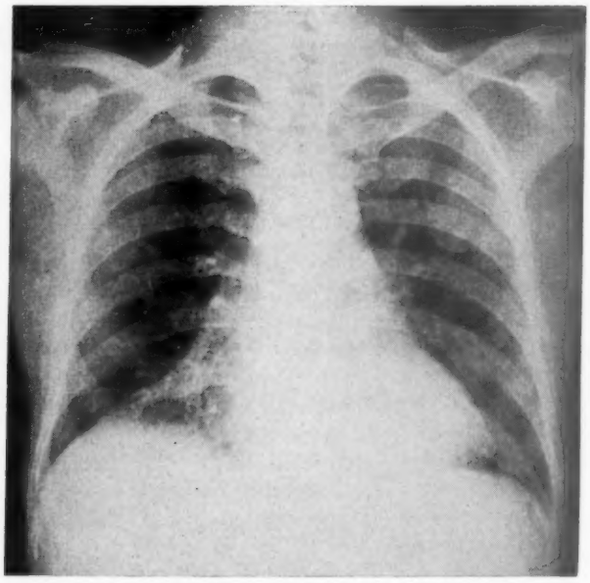
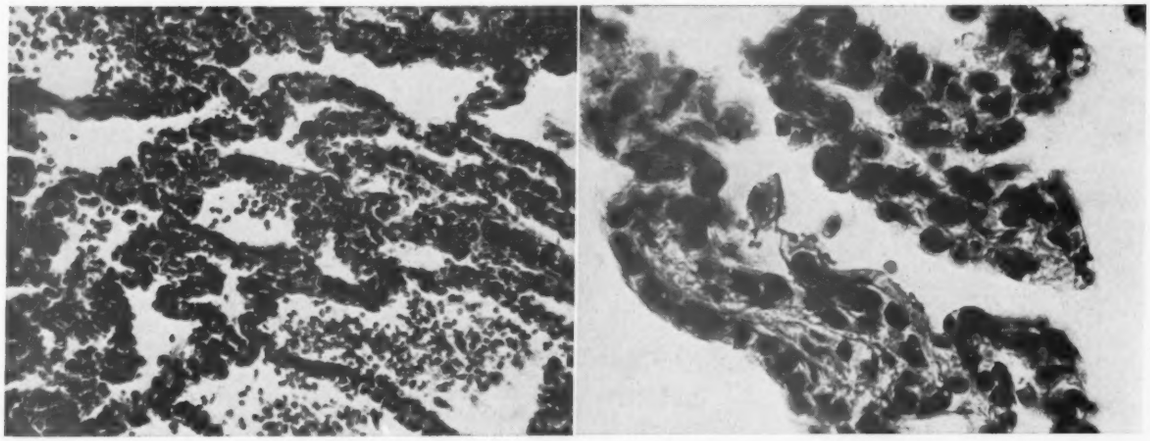


FIG. 4. Posteroanterior roentgenogram of the chest taken on January 22, 1959 (six weeks after Fig. 2), following antileukemic chemotherapy and x-ray radiation of the chest showing reduction in the transverse diameter of the heart and complete resolution of the lymphadenopathy and interstitial infiltrates. The interstitial markings are slightly prominent.



5A 5B

FIG. 5. A, diffuse thickening of alveolar walls due to leukemic infiltration. Hematoxylin and eosin, original magnification × 180. B, higher magnification showing heavy infiltration of alveolar walls by leukemic cells. One capillary is filled with leukemic cells. Trichrome stain, original magnification × 380.

gm. per 100 ml.; and the hematocrit was 48 per cent. There were 200,000 platelets per cu. mm. The bone marrow was hypercellular. Sixty-eight per cent of the cells were blasts or primitive undifferentiated cells many of which contained granules on peroxidase staining. A diagnosis of acute myelomonocytoid leukemia was made. Roentgenographic examination of the chest (Fig. 4) did not show any definite abnormalities. Urinalysis showed many hyaline casts. The serum bilirubin, blood urea nitrogen and uric acid were normal. An electrocardiogram showed minor nonspecific changes.

The patient lived for thirty-three days following hospitalization. He was treated with 300 mg. of 6-mercaptopurine daily. Three hundred mg. of methylprednisolone daily was added to this regimen and finally 2 mg. of aminopterin daily. Twenty-six days after admission the white blood count was 306,000 per cu. mm. and the platelet count 24,000 per cu. mm. The uric acid was 9.6 mg. per cent. Clinical deterioration progressed with increasing dyspnea, tachypnea, tachycardia, sweating, anorexia and weight loss. Two days before death, petechiae and purpuric lesions appeared.

Postmortem examination revealed a well nourished body, covered with petechial hemorrhages. There was complete obliteration of both pleural spaces and the pericardial sacs by thin fibrous adhesions. There was generalized enlargement of the lymph nodes. The liver and spleen were adherent to the diaphragm. The spleen weighed 950 gm., the liver 2,850 gm. The bone marrow appeared hyperplastic. The heart weighed 425 gm. The subendocardial surface of the left ventricle was diffusely hemorrhagic with some extension of the hemorrhage into the underlying myocardium. All cardiac chambers were dilated. The lungs together weighed 1,450 gm. The upper lobes appeared normal. The lower lobes were reddish brown and felt diffusely indurated. The rest of the organs were within normal limits.

Microscopic examination of the bone marrow revealed marked hypercellularity due to proliferation of blast and primitive cells. There was slight differentiation into recognizable granulocytes. Erythropoiesis was practically absent. The lymph nodes were almost completely replaced with leukemic cells. There was also leukemic infiltration of the spleen and liver. The hemorrhage in the subendocardial myocardium was without inflammatory reaction. The pericardium and epicardium were fused and thickened by fibrous tissue. Of particular interest was the microscopic appearance of the lungs. (Fig. 5.) The alveolar septums were greatly thickened by interstitial leukemic infiltration and the pulmonary capillaries were congested with leukemic cells. There were scattered areas of bronchopneumonia.*

STUDIES OF PULMONARY FUNCTION

Because of the presence of dyspnea and tachypnea and the history of pulmonary infiltrates, studies of pulmonary function were made on January 29, 1959. (Tables I, II, III and Fig. 6.) The details of the technics used in our laboratory have been previously reported [*5*]. There was no definite roentgenographic evidence of lung disease (Fig. 4) at that time. The studies, however, demonstrated the classic pattern of restrictive lung changes and alveolar-capillary block with no evidence of airway obstruction. The lung volumes (Table I) were reduced but the

* We are grateful to Dr. Philip V. Skerrett, Assistant Chief of the Pathology Service, Philadelphia Veterans Administration Hospital for examination and interpretation of the pathologic material.

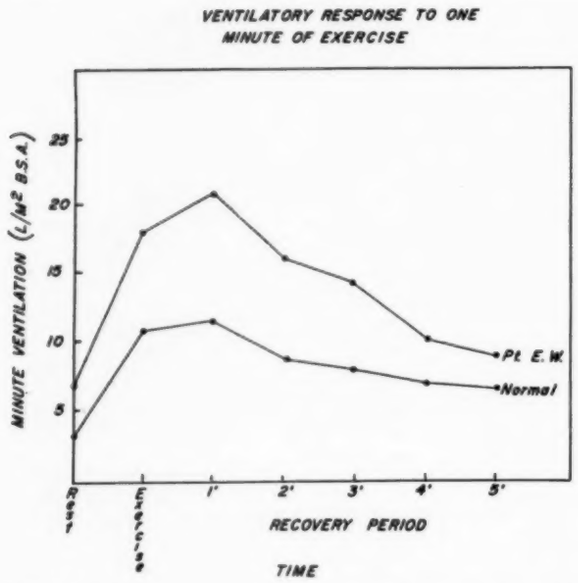


FIG. 6. Hyperventilation was present in the resting basal state and there was an exaggerated ventilatory response to one minute of exercise.

timed vital capacity and maximum breathing capacity were normal. The resting respiratory rate was 26 per minute and the volume of ventilation per square meter of body surface area was 6.77 L. per minute (normal 3 to 4 L. per minute per square meter of body surface area). The ventilatory response to exercise was exaggerated. (Fig. 6.) The resting arterial oxygen saturation was 83.8 per cent and dropped to 69.4 per cent following one minute of exercise. (Table II.) The arterial carbon dioxide content, pH and carbon dioxide tension were within normal limits. Oxygen diffusion studies were performed by the technic of Riley, Proemmel

TABLE I
LUNG VOLUMES AND VENTILATORY STUDIES

Study	Predicted Normal	Patient	Per cent of Predicted
Inspiratory capacity (L.)	4.00	1.71	43
Expiratory reserve volume (L.)	1.00	0.85	85
Vital capacity (L.)	5.00	2.55	51
Residual volume (L.)	1.60	1.52	95
Total lung capacity (L.)	6.60	4.07	62
R.V./T.L.C.	0.24	0.37	...
One second vital capacity (per cent of total)	>70	86	...
Three second vital capacity (per cent of total)	>90	100	...
Maximum breathing capacity (L./min.)	128	176	138
Respiratory rate per minute	12	26	216
Minute ventilation (L./M² B.S.A.)	3.50	6.70	191

TABLE II
ARTERIAL BLOOD STUDIES

Study	Normal Resting Values	20.89% O_2	100% O_2	Immediately After One Minute Exercise
Oxygen saturation (per cent)	>92	83.8	100 + 0.98 ml.	69.4
CO_2 content (volume per cent)	48–52	50.8	49.4	48.4
pH	7.37–7.42	7.37	...	...
CO_2 tension (mm. Hg)	38–44	44	...	...

TABLE III
DIFFUSION STUDIES

Condition	Inspired pO_2 (mm. Hg)	Alveolar pO_2 (mm. Hg)	Arterial pO_2 (mm. Hg)	I-A* Gradient (mm. Hg)	A-a† Gradient (mm. Hg)	Physiologic Dead Space (ml.)
20.89% O_2	151	104	64	47	40	194
14.99% O_2	108	69	56	39	13	195

NOTE: Oxygen diffusing capacity (ml./min./mm. Hg): 12 (normal: >15).
* Gradient in oxygen tension between inspired air and alveolar air.
† Gradient in oxygen tension between alveolar air and arterial blood.

and Franke [*6*] for determination of the oxygen tension of blood and the method of Riley, Cournand and Donald [*7*] for analysis of gas exchange relationships. The presence of a diffusion defect was confirmed. (Table III.)

COMMENTS

An impediment to the diffusion of oxygen across the alveolar-capillary interface can be produced by any disease which involves the interstitial area of the pulmonary parenchyma and thickens or alters the characteristics of the alveolar-capillary membrane. It is not surprising, therefore, to find a growing list of unrelated diseases that have been reported to produce the alveolar-capillary block syndrome. Among them are beryllium granulomatosis, sarcoidosis, scleroderma, other collagen vascular diseases, asbestosis, diffuse pulmonary lymphangitic carcinomatosis, miliary tuberculosis, the Hamman-Rich syndrome, histocytosis X, Farmer's lung, Silo-Filler's Disease, mitral stenosis, pulmonary edema, emphysema, pulmonary fibrosis, silicosis, alveolar cell carcinoma, sulphur dioxide poisoning and pulmonary eosinophilia [*8–11*]. In its fully developed form, of which our patient is a good example, the syndrome is characterized by dyspnea aggravated by minimal exertion, tachypnea, hyperventilation, an exaggerated ventilatory response to exercise, restrictive lung changes with reduced lung volumes, no evidence of airway obstruction, resting arterial oxygen unsaturation aggravated by exercise, and a reduction in the oxygen diffusing capacity. Despite the diffusion defect for oxygen, carbon dioxide retention does not occur because this gas is approximately twenty times more diffusible than oxygen. The postmortem demonstration in our patient of extensive leukemic infiltration of the alveolar capillary area closely correlates morphology with pathophysiology.

Leukemia involves the lungs in 25 per cent of autopsy cases [*1–3*]. The sites of involvement are peribronchial, perivascular, pleuritic and interstitial [*1*]. Estimates of the incidence of interstitial infiltration range from 4 to 15 per cent, but involvement sufficiently extensive to produce symptoms and disturb pulmonary function probably occurs in less than 3 per cent of patients [*1,2*]. The possibility of an alveolar-capillary block syndrome due to leukemia has been suggested previously on the basis of clinical and pathologic evidence [*1,4*], but to the best of our knowledge this is the first case in which detailed studies of pulmonary function have demonstrated the fully developed syndrome. It is of interest that there was no roentgenographic evidence of pulmonary involvement at the time the studies were performed, although the patient was quite dyspneic. This suggests that the leukemic infiltrates, although extensive and diffuse, were not sufficiently discrete or nodular to produce a shadow on the roentgenogram.

SUMMARY

A patient with acute myelogenous leukemia is described whose chief complaint during most of his illness was dyspnea. Detailed studies of pulmonary function demonstrated the fully developed pathophysiologic derangement of an "alveolar-capillary block." Postmortem examination revealed extensive leukemic infiltration of the alveolar-capillary interface.

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Diffuse Interstitial Pulmonary Fibrosis (Hamman-Rich Syndrome)*

A Correlation of Clinical, Physiologic, Roentgenologic and Pathologic Findings in a Patient Studied for Three Years, Before and After Adrenocorticosteroid Treatment

BRIGITTE B. NAHMIAS, M.D.,† A. GRIGG CHURCHWELL, M.D. *and* F. NORMAN BOWLES, M.D.
Atlanta, Georgia

We have recently had the opportunity to study a young patient with the Hamman-Rich syndrome during the three-year course of his disease. It was possible to observe the natural course of the disorder over a period of one year and to obtain detailed pulmonary function tests, as well as numerous other data. Confirmation of the diagnosis and correlation of pathologic with physiologic findings was made possible by an open biopsy. Treatment with adrenocorticosteroids was then instituted. The results of therapy and the patient's course were evaluated clinically, physiologically and roentgenologically until the patient's death two years later, at which time a final pathologic examination was performed.

CASE REPORT

A seventeen year old Negro student was admitted to Grady Memorial Hospital in March 1957. He had been in good health until about six months prior to admission when he noted the onset of mild but progressive dyspnea on exertion, as well as dry cough and easy fatigability. Two weeks prior to admission these symptoms had increased in severity and low grade fever had appeared.

The past history and family history were noncontributory. The patient had spent most of his life in Georgia, with brief visits to New York, Washington, D. C. and Tennessee. There was no known exposure to infectious diseases, toxins, dusts, fumes or broken fluorescent light bulbs.

On physical examination the patient appeared to be a well developed and rather lean young man in no distress. He had, however, an increased respiratory rate of 38 per minute. The breath sounds were harsh in both lung fields and fine rales were heard at the base of the right lung. The fingers showed minimal clubbing but no cyanosis. No other significant abnormalities were found. The temperature, which was 101°F. on admission, became normal on the next day and remained so thereafter.

A chest roentgenogram obtained at the local health department at the time of onset of symptoms showed a fine, reticular fibrosis in the right infra-clavicular and mid-lung fields, with less involvement of the lower lung field. The left lung appeared normal and there was no hilar adenopathy. This film, unfortunately, is no longer available for photography.

The chest roentgenogram on admission (Fig. 1A) showed the reticulogranular fibrosis now located more inferiorly, in the right intermediate and lower lung fields. A 7 cm. diameter area of rarefaction was noted within the fibrotic pattern and, after being outlined with tomograms, was considered to be an air-filled cyst. The left lung field was essentially clear. The heart was in the midline and of no unusual configuration except for some prominence of the pulmonary artery segment. The descending branch of the right pulmonary artery measured 14 mm. in diameter. There was no hilar adenopathy and the diaphragms appeared normal. No unusual masses were visible in the abdomen. Roentgenograms of the hands were within normal limits.

Laboratory studies included a normal urinalysis and a negative reaction to the serologic test for syphilis. The hematocrit was stable at 45 per cent and the white blood count ranged from 3,950 to 5,300 per cu. mm. with a normal differential. The serum total protein was 7.8 gm. per cent, the albumin 2.9 gm. per cent and the globulin 4.9 gm. per cent. Serum protein electrophoresis revealed a low albumin and increased

* From the Department of Internal Medicine and the Cardio-Pulmonary Laboratory, Emory University School of Medicine; and the Medical and Pathological Service, Grady Memorial Hospital, Atlanta, Georgia.
† Present address: Boston City Hospital, Boston, Massachusetts.

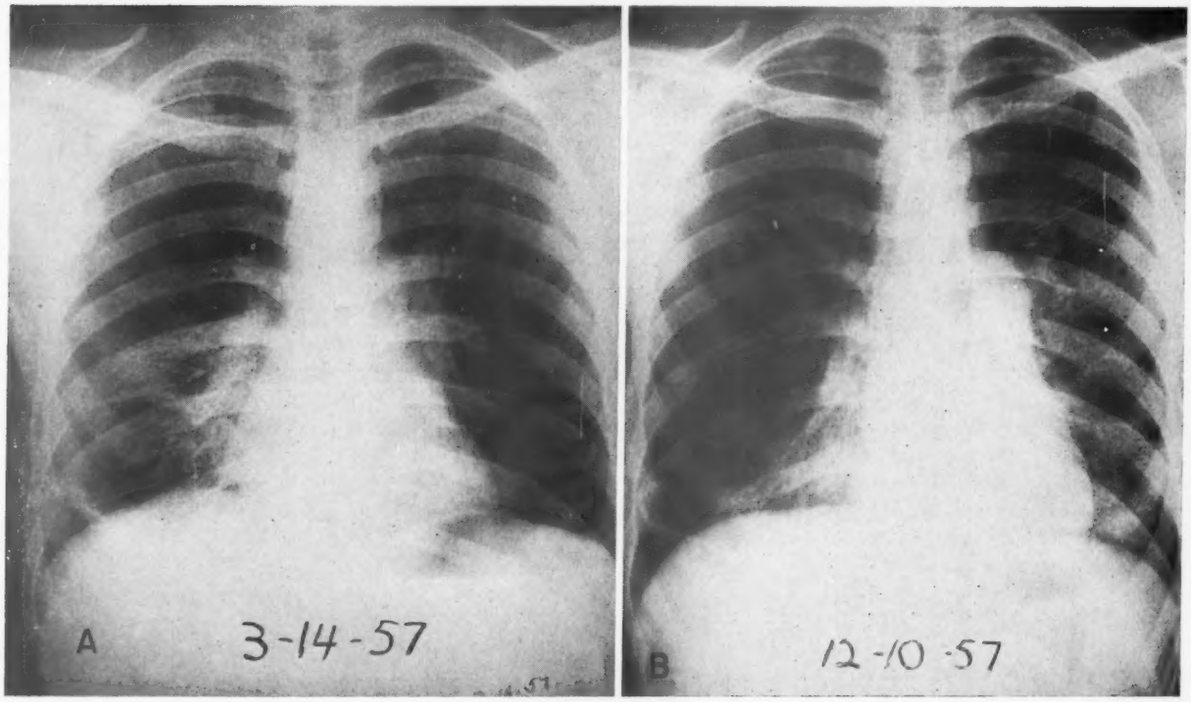

FIG. 1. Chest roentgenograms. A, first admission. Note the reticulogranular fibrosis in the right mid- and lower lung fields. B, second admission. Note the appearance of the fibrosis in the left lung field, the increase in emphysema peripherally, and the clockwise rotation of the heart.

alpha and gamma globulins. Blood calcium, phosphorus and alkaline phosphatase were normal. Blood agglutination tests were negative for S. typhosa O; 1:40 for S. typhosa H; and negative for brucella, typhus (Weil-Felix reaction), S. paratyphi A and B, and P. tularensis. The cold agglutinin test was negative. The heterophil agglutinin test was positive at 1:56, and one week later was positive at 1:28 with partial agglutination at 1:56.

The sputum smear showed some gram-positive cocci and diplococci and many polymorphonuclear neutrophils. Three cultures grew "usual mouth flora." Cultures for M. tuberculosis and fungi were negative. Blood cultures were also negative. The bone marrow smear was entirely normal and cultures for M. tuberculosis were negative. Skin tests with histoplasmin, coccidioidin and purified protein derivative tuberculin first and second strength gave negative reactions.

The electrocardiogram was normal. Bronchoscopy revealed slight edema of the bronchus of the lower lobe of the right lung and some secretions. Bronchial washings produced a proteinaceous coagulum; cultures for M. tuberculosis and fungi were negative.

The patient received general supportive care and on April 1, 1957, when he had recovered from the acute episode, lung function tests were performed. (Column 2 in Table 1.) These revealed a moderate restrictive defect with a small total lung capacity and vital capacity, an abnormal distribution of inspired gases and a large ventilation. Resting arterial blood gases were normal, but with exercise there was a fall in arterial pO_2 and a rise in the alveoloarterial O_2 gradient.

The patient felt improved, and it was decided to follow him closely in the outpatient clinic, where he was treated with expectorants and bronchodilators. However, he was lost to follow-up until eight months later (December 1957) when he was re-admitted to the hospital with an increase in exertional dyspnea and non-productive cough, as well as a 9 pound weight loss. Six weeks prior to admission he had suffered an influenza-like illness with fever, chills and malaise, which had been treated with penicillin and subsided in ten days. He had to discontinue his schooling since then.

On physical examination he was noted to have mild cyanosis and some increase in clubbing of the fingers. The lung findings were unchanged. The heart was noted to have a loud, split P_2 and there was a precordial lift. The results of extensive laboratory studies were essentially unchanged. Results of complement fixation tests for histoplasmosis and blastomycosis were negative, as well as skin tests.

The chest roentgenograms (Fig. 1B) had changed significantly. The fibrotic pattern on the right had retracted or had been pushed toward the midline and the peripheral lung field showed a distinct absence of vascular markings, giving the appearance of

TABLE 1

PULMONARY FUNCTION TESTS

Test	Normal	6 Months After Onset (4/1/57)	14 Months After Onset (12/10/57)	3 Weeks After Treatment (2/18/58)	10 Weeks After Treatment (4/8/58)	7 Months After Treatment (8/26/58)	1 Year After Treatment (1/20/59)	2 Years After Treatment (12/9/59)
Lung Volumes								
Vital capacity (ml.)	4,400	2,200 = 50%*	1,593 = 36%	2,194 = 50%	2,780 = 63%	2,568 = 58%	2,835 = 64%	3,021 = 68%
Inspiratory capacity (ml.)		1,191	891	1,258	1,744	1,498	1,284	1,805
Expiratory reserve volume (ml.)		1,001	702	936	1,036	1,070	1,551	1,216
Residual volume (ml.)	1,100	1,282 = 117%	2,009 = 182%	...	2,237 = 200%	2,031 = 185%	1,715 = 154%	...
Total lung capacity (ml.)	5,500	3,482 = 63%	3,602 = 65%	...	5,017 = 91%	4,599 = 84%	4,550 = 82%	...
Functional residual capacity (ml.)		2,283	2,711	...	3,273	3,101	3,266	...
Ratio: R.V./T.L.C. (%)	30	37	56	...	45	44	38	...
Mechanical Function								
Maximum breathing capacity (L./M²/min.)	77.6	80.3 = 103%	55.5 = 72%	62.5 = 81%	77.8 = 101%	71.5 = 93%	71.4 = 93%	50.0 = 65%
Timed vital capacity, 1 sec. (%)	83	49	40	45	...	56	51	53
Timed vital capacity, 3 sec. (%)	95	88	86	100	100	99	100	77
Distribution of Inspired Gas								
Single breath N_2 (%)	2.0	4.0	6.0	4.0	4.0	10.0	7.5	5.0
N_2 washout, 7 min. (%)	2.5	1.2	2.0	...	2.3	2.9	1.8	...

Ventilatory Function

		Air	15% O_2	Exercise	Air	15% O_2	Exercise	Air	Exercise	Air	15% O_2	Exercise	Air	15% O_2	Exercise	Air	15% O_2	Exercise	Air	15% O_2	Exercise
Respiratory rate (min.)	12	38	37	53	22	20	66	18		14	16		15			15	16		...		
Respiratory depth (ml.)	500	283	319	579	535	1.06	601	481		607	515		298			382	396		...		
Respiratory minute ventilation (L./M²)	3.4	6.5	7.1	18.7	7.4	13.4	24.9	5.4		5.4	5.2		2.9			3.6	4.4		...		
Respiratory dead space (ml.)	125	160	133	210	250	645	212	277		356	228		168			103	...		...		
Alveolar minute ventilation (L./M²)	2.0	2.8	3.0	10.2	2.8	4.6	14.1	1.5		2.9	2.8		0.82			2.1	...		...		
Respiratory quotient	.85	0.81	0.96	0.96	0.76	1.0	0.71	0.85		0.92	0.67		0.87			0.82	...		...		
Arterial Blood Studies																					
O_2 saturation (%)	95	95	77	91	82	54	60	86	72	93	78	81	92†	76	73	95	77	69	...		
pH	7.40	7.39	7.46	7.37	7.44	7.50	7.36	7.45	7.42	7.47	7.46	7.44	7.42	7.50	7.41	7.45	7.46	7.37	...		
CO_2 content (mEq./L.)	21.3	21.6	21.1	20.1	16.8	20.0	16.7	19.2	19.2	19.2	18.8	19.2	18.7	18.0	18.0	19.6	19.0	18.3	...		
Hemoglobin (gm. %)	14	12.3	12.4	12.3	15	...	...	14.0	15.0	12.9	12.9	13.5	14	...	...	13	...	...	...		
pO_2 (mm. Hg)	80	75	52	64	47	...	33	61	41	68	44	48	64	43	42	57	38	36	...		
pCO_2 (mm. Hg)	40	40	35	38	34	31	31	38	38	37	33	40	38	35	38	36	36	38	...		
Alveolar pO_2 (mm. Hg)	95	96	66	104	101	65	102	102	...	104	56	...	100	...	...	102	...	...	...		
Alveolo-arterial O_2 gradient (mm. Hg)	15	21	14	40	54	...	69	41	...	36	12	...	36	...	...	45	...	...	...		

* Per cent of normal.
† O_2 saturation after ten minutes of 100 per cent O_2 breathing: 104%.

TABLE II

LUNG FUNCTION TESTS DURING THE NATURAL COURSE OF THE DISEASE

Test	6 Months After Onset			14 Months After Onset		
	Rest	Exercise	15% O_2	Rest	Exercise	15% O_2
Minute ventilation (L./M²)	6.5	18.7	7.1	7.4	24.9	13.4
Arterial pCO_2 (mm. Hg)	40	38	35	34	31	31
Arterial O_2 saturation (%)	95	91	77	82	60	54
Alveolo-arterial O_2 gradient (mm. Hg)	21	40	14	54	69	...

emphysema. The cystic area had decreased in size. The mediastinum had shifted toward the left. In the left lung field there was also a striking change, the reticulogranular fibrotic infiltrate now appearing in the entire mid- and lower lung fields. The heart had rotated clockwise and the descending branch of the right pulmonary artery had increased to an 18 mm. diameter. The electrocardiogram now showed a marked shift of the mean QRS vector to the right, compatible with right ventricular hypertrophy.

Concomitantly with the deterioration in clinical radiographic and electrocardiographic aspects, there was marked worsening in pulmonary function. The vital capacity had fallen to 36 per cent of normal. At the same time the speed of expiration had decreased and the maximum breathing capacity had fallen to 58 per cent of normal. Table II summarizes the most striking changes in other aspects of lung function. It is apparent that at the time of the first admission the minute ventilation was quite large, and that with such effort the patient was able to maintain a normal resting oxygen saturation. However, eight months later, despite an even larger ventilation (enough to lower his pCO_2 to 34 mm. Hg), the patient could no longer maintain a normal O_2 saturation. There was a marked drop in arterial O_2 saturation during exercise and during 15 per cent O_2 breathing, along with a rise in the alveoloarterial O_2 gradient during exercise. Cardiac catheterization revealed moderate increase in mean pulmonary artery pressure.

Following these studies an open thoracotomy was performed, with lung biopsy. At the time of surgery it was noted that the surface of the left lung was covered with small blebs, 1 to 5 mm. in diameter, which inflated and deflated with every breath. The lung generally felt crepitant. A biopsy specimen, removed from the tip of the lingula, felt firm and meaty in consistency and was light tan in color. Microscopically (Fig. 2), the pleura was slightly thickened. The underlying pulmonary parenchyma showed prominent thickening of the alveolar septums by collagenous tissue and by cellular proliferation. The cells varied from plump fibroblasts to fairly uniform cells which were probably histiocytic in type. The epithelial lining of the alveoli showed marked metaplasia, with cells varying from the usual flat cuboidal to high cuboidal and frank columnar. The alveolar spaces were large and irregular, with numerous ruptured alveolar septums, producing a somewhat papillary appearance in some areas. Many alveolar spaces contained large histiocytes. Bronchioles in the

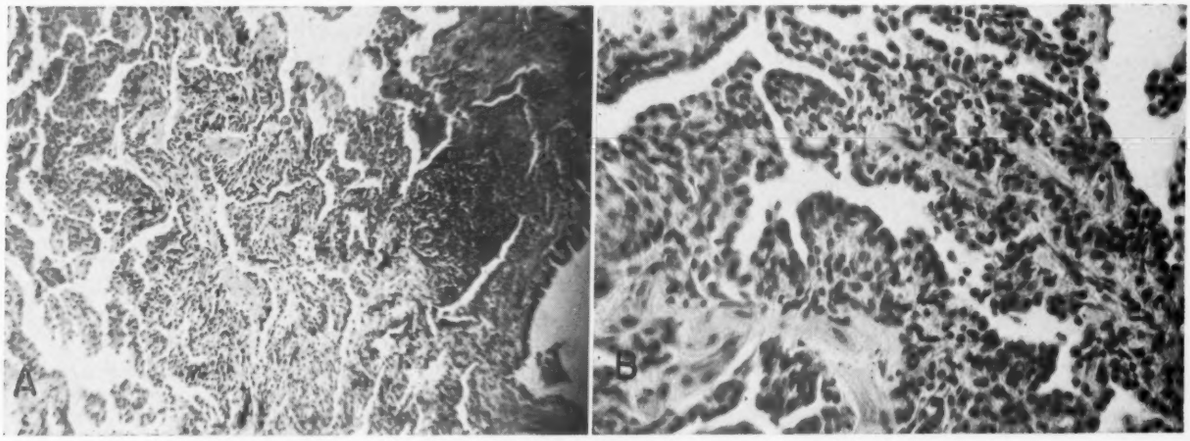

FIG. 2. Photomicrograph of lingular biopsy showing fibrous thickening of alveolar septums and metaplasia of alveolar lining cells. Hematoxylin and eosin. A, magnification × 60. B, magnification × 140.

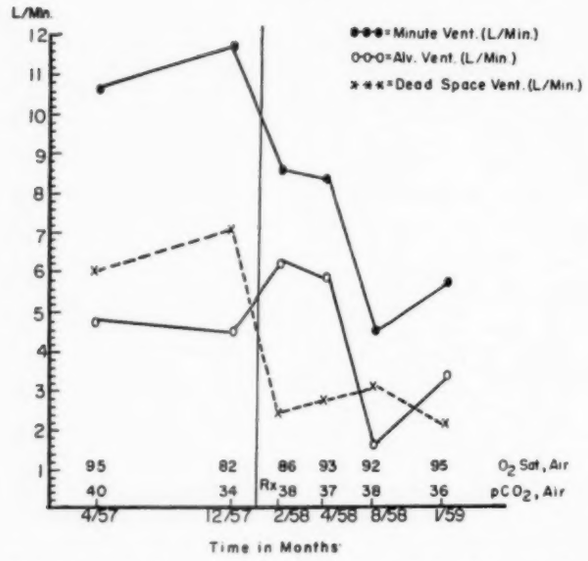
L/Min.
●●●=Minute Vent. (L/Min.)
○○○=Alv. Vent. (L/Min.)
×××=Dead Space Vent. (L/Min.)
95 82 86 93 92 95 O_2 Sat., Air
40 34 38 37 38 36 pCO_2, Air
Rx
4/57 12/57 2/58 4/58 8/58 1/59
Time in Months

FIG. 3. Ventilatory function before and after corticosteroid therapy. The vertical line indicates onset of therapy. Note the sharp drop in minute ventilation after treatment.

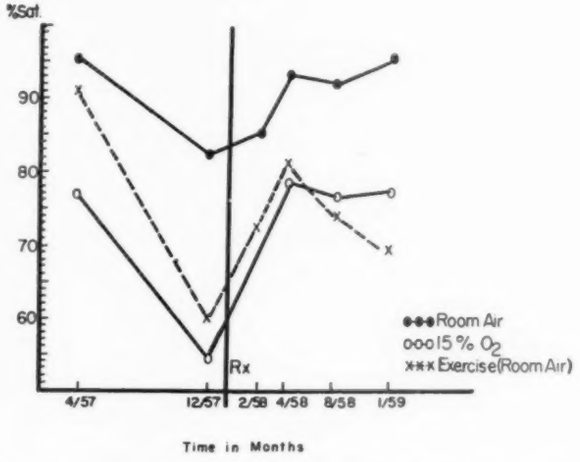

FIG. 4. Arterial oxygen saturations before and after corticosteroid therapy. The vertical line indicates onset of therapy. Note the rise in O_2 saturation on room air breathing after treatment, but also the fall on exercise in the later studies.

area appeared somewhat dilated and the walls of blood vessels showed moderate fibrous thickening particularly involving the sub-intimal layer. An occasional large lymphocytic aggregation was noted, but there was no other evidence of inflammation.

The pathologic findings were considered to be compatible with the clinical and physiological studies and the definitive diagnosis of interstitial pulmonary fibrosis of the Hamman-Rich type was made.

In January 1958 adrenal corticosteroid therapy was begun. The patient received prednisone, 20 mg. per day, for several months and was then maintained on 15 mg. per day for the rest of his life. The clinical course on this therapy was characterized by definite improvement, manifested by a decrease in symptoms to the point that the patient was able to return to school and to play baseball (but with someone else running bases). This improvement was maintained for one year.

The physiologic course is given in detail in Table I. There was a marked rise in all lung volumes and in maximum breathing capacity, back to the originally recorded levels. The ventilatory function is illustrated by Figure 3. It can be seen that after treatment there was a striking fall toward normal in the minute ventilation, as well as in dead space ventilation. The concomitant arterial O_2 saturations are also listed below the points of the graph. It is clear that the patient's O_2 saturation improved as his ventilation dropped. The arterial O_2 saturations are illustrated in Figure 4. Again a notable improvement is seen after treatment, maintained for one year. Roentgenographically and electrocardiographically, there was little change during this year.

Following this period of clinical and physiological improvement there was a slow and insidious deterioration in the patient's clinical condition. On careful questioning an increase in dyspnea on exertion could be elicited, and on physical examination intermittent wheezing could be detected by auscultation. Six months later symptomatic right ventricular failure developed, manifested chiefly by painful and tender hepatomegaly. There was prompt compensation in response to the administration of digitalis and diuretics, but thereafter cardiac decompensation recurred frequently and several respiratory infections supervened. Clubbing and cyanosis became more apparent and the hematocrit rose. The serum total proteins were 7.4 gm. per cent, with an albumin of 4 gm. per cent and a globulin of 3.4 gm. per cent. Liver function tests showed mild impairment compatible with chronic congestion.

The patient was re-admitted to the hospital for the third and last time in December 1959, three years after onset of symptoms and two years after diagnosis and institution of corticosteroid therapy. Over a period of three days, marked increase in dyspnea had developed, associated with nausea and pain in the right upper quadrant. He was noted to be desperately ill, cyanotic and breathing shallowly at a rate of 64 per minute. The pulse was 130 per minute and the blood pressure 115/76 mm. Hg. The neck veins were distended and pulsating, the liver edge was palpable and tender 4 fingerbreadths below the right costal margin. There was no ascites or pedal edema. Breath sounds were harsh, and crepitant rales were heard at the bases. The heart was enlarged and had a loud, split P_2 and a ventricular gallop rhythm.

The venous pressure was 246 mm. water and the arm-to-tongue circulation time (Decholin®) twenty-

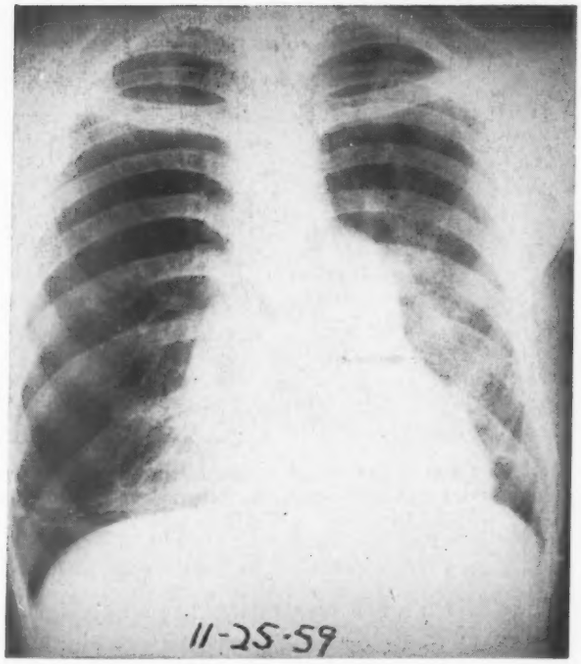

FIG. 5. Chest roentgenogram one month before death. Note the increase in heart size, the prominent pulmonary arteries and the increase in peripheral emphysema.

six seconds. The hematocrit was 56 per cent and the white blood count 13,200 per cu. mm. with 88 per cent polymorphonuclears. The blood urea nitrogen and electrolytes were normal, except for a CO_2 content of 10.7 mEq. per L.

The patient died within seven hours, despite vigorous treatment with digitalis, oxygen, intermittent positive pressure breathing, bronchodilators, diuretics, hydrocortisone, penicillin and a small phlebotomy.

Chest roentgenograms during the last years of life (Fig. 5) showed progressive development of peripheral emphysema in the lung fields and increasing heart size with a prominent pulmonary artery segment. The descending branch of the right pulmonary artery measured 21 mm. in diameter on the last roentgenogram. The electrocardiogram, concomitantly with the development of clinical heart failure, showed a further shift of the mean QRS vector to the right and anteriorly, as well as ischemic T wave changes. Five days prior to death, physiologic studies revealed an unchanged vital capacity (Table 1), inspiratory capacity and expiratory reserve volume. The maximum breathing capacity, however, had dropped to 65 per cent of normal. The distribution of inspired air was uneven, as it had been throughout the patient's course. Unfortunately, arterial blood studies, having been deferred on numerous occasions due to cardiac decompensation or intervening respiratory infection, were not obtained during the last year of his life.

At necropsy the body was that of a thin Negro man

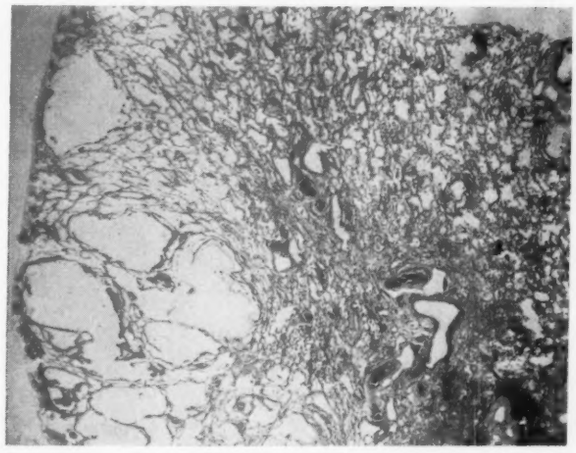

FIG. 6. Photomicrograph of lung at autopsy, hematoxylin and eosin stain, showing blebs beneath the pleura and prominent fibrosis nearer the hilus.

weighing approximately 110 pounds and measuring 169 cm. in length. There was no evidence of "Cushingoid facies," striae, or other stigmata of prolonged corticosteroid therapy. The distal phalanges of the fingers and toes were clubbed and cyanotic. There was a well healed left anterolateral thoracotomy scar. Examination of the body cavities revealed fibrous adhesions over the left lung in the area of previous surgery and at the base of the lower lobe. There was no free pleural or peritoneal fluid. There were no pericardial or peritoneal adhesions. The pericardial sac contained 300 cc. of amber fluid.

The heart weighed 450 gm. There was marked right ventricular hypertrophy and dilatation. The right ventricular myocardium measured 8 mm. in thickness and was firm. The left ventricle appeared to be normal. The pulmonary valve measured 8 cm. in circumference and the aortic valve 6.2 cm. There was no scarring or deformity of the valves. The endocardium and epicardium were smooth and glistening. The coronary arteries showed no abnormalities.

The lungs had a combined weight of 1,300 gm. and held their shape when removed. The interlobular septum were depressed when the lungs were inflated. The lungs were fixed in the inflated state by cannulating the trachea and instilling the tracheobronchial tree with 10 per cent buffered formalin under hydrostatic pressure. After fixation for three weeks they were sectioned transversely. There was marked bullous emphysema at the apices, at the periphery of all lobes, and in the lower lobe of the right lung, with bullae measuring up to 4 cm. The usual feathery structure of the pulmonary parenchyma was transformed into a honeycombed structure. (Fig. 6.) The bullae were separated by fibrous bands. Centrally the parenchyma was more firm, airless and granular. The bronchi and blood vessels appeared more prominent than usual. The bronchial lumens were empty and were not dilated. The major

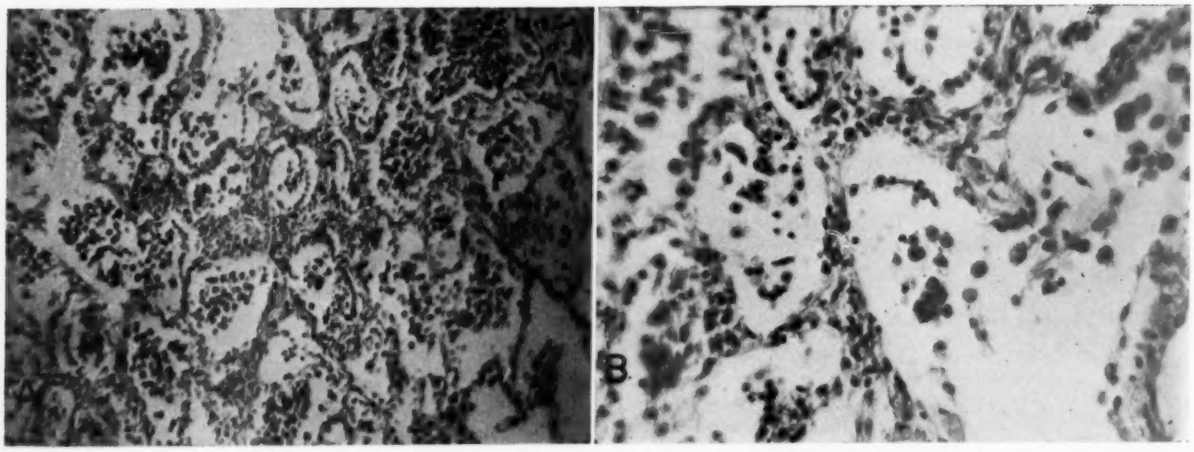

FIG. 7. Photomicrograph of lung at autopsy showing mature fibrous tissue in the alveolar septums, marked alveolar lining cell metaplasia, and macrophages within the alveoli. Hematoxylin and eosin stain. A, magnification × 60. B, magnification × 140.

branches of the pulmonary arteries showed small flat yellow plaques on the intimal surface.

The liver was firm. The central areas of the lobules were pale yellow and contrasted with the pinkish tan of the remainder of the parenchyma. The adrenals weighed 10 gm. each and did not show any abnormalities. The kidneys, spleen, pancreas, thyroid, gallbladder, lymph nodes, genitalia and gastrointestinal tract were within normal limits. The central nervous system was not examined.

Microscopically, the heart showed a moderate amount of interstitial fibrosis and slight fibrous thickening of the endocardium of the right ventricle.

Twenty sections of lung were studied from different lobes. They were stained with hematoxylin and eosin, Masson's trichrome and Verhoff's elastic tissue stain. There was fibrous thickening of the pleura and interlobular septums with aggregates of lymphocytes and a few plasma cells. In the alveolar septums there was a marked proliferation of fibroblasts. (Fig. 7.) In some areas the fibroblasts were long and thin, and were dispersed in collagen, in other areas they were plump, with less collagen, and suggested an active proliferative process. This proliferation of fibrous tissue thickened the septums and in some areas seemed to compress the capillaries which in general were engorged and prominent. In the more peripheral areas of the lung, emphysema was striking and there was less obvious septal thickening. In areas of marked fibrosis the alveolar lining cells appeared hypertrophied, giving a pseudoglandular appearance with closely packed cuboidal to columnar cells. There were small round cells throughout the fibrous tissue but this was not a prominent finding. The alveoli contained an occasional "hyaline" membrane and numerous macrophages with engulfed dust and hemosiderin. The bronchi showed an increase in the muscular coat and surrounding fibrous tissue. There was squamous metaplasia in a few bronchioles. The vessels showed thickening in all three layers and particularly in the subintimal and adventitial layers. There was no increase in elastic tissue in the lung.

The liver was the site of central hemorrhagic necrosis with centrilobular extravasation of red blood cells and polymorphonuclear infiltration. There was hemosiderin deposition in the Kupffer cells. There was no marked increase in fibrous tissue. The adrenals showed thinning of the cortex but no specific abnormalities. The kidneys and remainder of the organs were within normal limits.

METHODS

Most lung volumes, as well as the maximum breathing capacity and timed vital capacities, were obtained on a 9 L. Collins spirometer. The functional residual capacity, residual volume and index of pulmonary mixing were measured by the open circuit nitrogen dilution method. The uniformity of distribution of inspired air was measured by the continuous N_2 analysis of an expiration, following a single breath of oxygen. Ventilatory gases were collected in a Douglas bag and measured through a Wet Test gas meter. Expired gases were analyzed by the micro Scholander technic. Arterial blood was obtained from the brachial artery and analyzed for O_2 saturation and CO_2 content by the manometric method of Van Slyke and Neill. The pH was measured with the Cambridge pH meter. The arterial O_2 and CO_2 tensions were determined by the direct bubble method of Riley. The exercise test consisted of raising and lowering the legs in a supine position for five minutes and blood was obtained during the fifth minute. Physiologic dead space and alveolar ventilation were calculated from the Bohr equation, using arterial pCO_2 as equal to alveolar pCO_2 [*1*]. The alveoloarterial O_2 gradient was determined by the Riley technic [*2*].

COMMENTS

At the time of the patient's first admission, six months after onset of symptoms, considerable lung involvement was already evident by symptoms, roentgenograms and pulmonary function tests. It also appears that there was, in all probability, some degree of pulmonary hypertension present, in view of the rather large pulmonary arteries evident on the roentgenogram. There was no obvious etiology for the fibrotic process, which has been variously ascribed to an unknown virus or fungus, air pollution, chronic pulmonary edema, toxins or hypersensitivity to one or several agents [*3,4*].

The progression of the disease, which was intermediate in rate between the more acute and a few very chronic cases described in the literature [*5*], is well illustrated by comparison of the findings at the time of the first and second hospital admissions. Three trends are evident.

The first is a progression in interstitial fibrosis, well demonstrated on the roentgenograms. The abnormal resting oxygen saturation despite a large minute ventilation, as well as the fall during exercise and 15 per cent O_2 breathing and the rise in the alveoloarterial O_2 gradient during exercise, are indicative, at least indirectly, of a diffusion defect of the "alveolocapillary block" type [*6*]. This could well be explained by the thickened alveolar lining and interstitium. Another explanation of the O_2 exchange abnormalities, especially during exercise, is that advanced by Luchsinger et al. [*7*] implicating loss of pulmonary capillary bed, with resulting precapillary pulmonary hypertension, and diminished air-blood contact time in the remaining capillaries as a result of increased flow through them.

The second trend is one of progressive emphysema, evident clinically by wheezing, and well demonstrated in the peripheral portions of all lobes in roentgenograms. At the same time the function tests reveal a slowing of expiration, a fall in the maximum breathing capacity, an abnormal distribution of air by the single breath test and an increase in residual volume with a greater ratio of residual volume to total lung capacity.

The third trend is progressive cor pulmonale, well demonstrated by increasing heart size, clockwise rotation of the heart, and increasing size of the pulmonary arteries. These findings are paralleled by the electrocardiographic changes of a shift to the right of the mean QRS vector, and the development of high peaked P waves. Cardiac catheterization confirmed the elevated pulmonary artery pressure.

All these findings correlate well with the pathology of the lung biopsy, which presents a picture of alveolar lining cell hyperplasia and interstitial proliferation of fibrous tissue, similar to that first described by Hamman and Rich in 1935 [*8*]. Some evidence of emphysema also is already apparent.

Divergent reports have been published concerning the safety and efficacy of treatment with adrenocorticosteroids [*3,5,9–19*]. In this patient there was significant clinical improvement for one year, corroborated by the pulmonary function tests. The rise in lung volumes and maximum breathing capacity probably indicates a decrease in the pulmonary interstitial reaction, although without pathologic study this cannot be attributed to any specific tissue component. Certainly the decrease in ventilation, with concomitant rise in arterial oxygen saturation, indicates much more efficient lung function with better gas exchange. But it is in these studies of arterial O_2 saturation that the first bad omen appears. It is possible that the progressive drop in O_2 saturation during exercise, noted in the later studies, was the first indication of functional progression of the disease, with further loss of the pulmonary capillary bed.

Several questions in regard to treatment are posed by this case. The first relates to the value of adrenocorticosteroids. In view of recent reports [*12–19*] and the experience in the present case, there can be little doubt that steroids may improve symptoms and function. Whether or not the duration of the disease is influenced is not known.

The second question relates to drug dosage. Insufficient data are available to make a rational choice between low-dose, long-term therapy or high-dose, short-term therapy, or various combinations. At present we tend toward high-dose, short-term initial treatment, with lower-dose, long-term maintenance thereafter.

The third question relates to the mechanism of action of the steroids. Certainly in this patient there must have been a change in the pulmonary interstitial reaction. There is great need for serial pathologic studies, relating treatment and functional changes with morphologic changes.

The fourth question relates to the time of onset of treatment. In this patient no improve-

ment was evident on the roentgenogram or electrocardiogram after treatment, indicating that much irreversible change had already taken place. The eventual deterioration in this patient's course can well be explained on the basis of progressive emphysema and cor pulmonale due to irreversible loss of pulmonary capillary bed, even if the activity of the pulmonary process were completely suppressed. However, the autopsy findings suggest that, in some areas, smoldering activity was still present. Certainly we would urge, in similar cases, performance of a lung biopsy as part of the diagnostic work-up, and institution of adrenocorticosteroid therapy at the earliest possible moment.

SUMMARY

We have described an extensively studied case of a young man with pulmonary interstitial fibrosis who exhibited a progressive course of fibrosis, emphysema and cor pulmonale for one year after onset of symptoms. Following diagnosis by lung biopsy and institution of adrenocorticosteroid therapy, he demonstrated clinical improvement for one year, corroborated by several detailed pulmonary function studies. Eventual deterioration, with death three years after onset of symptoms and two years after institution of therapy, is attributed to progressive emphysema and cor pulmonale.

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The Association of Pheochromocytoma with Carcinoma of the Thyroid Gland*

JOHN H. SIPPLE, M.D.†
Syracuse, New York

MULTIPLE neurofibromatosis is present in about 5 per cent of cases of pheochromocytoma, and there is suggestive evidence of an increased incidence of other associated neurocutaneous syndromes [*1,2*]. No association of pheochromocytoma with tumors of other organs has been established, but several authors have stated that there seems to be one [*3,4*].

In 1952 DeCourcy and DeCourcy [*4*] stated that "a considerable and, we believe, a significantly high percentage of patients with pheochromocytoma have had coexistent diffuse or nodular goiter or thyroid carcinoma." There are no other statements in the literature suggesting an increased incidence of carcinoma of the thyroid gland in pheochromocytoma. It is the purpose of this paper to report a case of pheochromocytoma and carcinoma of the thyroid and to present briefly five cases previously reported in which this association was present. It will be shown that although the over-all incidence of malignant tumors of other organs is not increased in pheochromocytoma, there is a significant incidence of carcinoma of the thyroid gland.

CASE REPORT

CASE 1. E. C., a thirty-three year old man, was admitted to the Syracuse Veterans Administration Hospital on April 17, 1959. Four hours before admission he had a severe right-sided headache, with nausea and vomiting. This was followed by left-sided weakness and lethargy. For many years he had occasionally experienced severe headaches. The results of previous blood pressure measurements were not known.

Examination revealed a blood pressure of 140/70 mm. Hg. The retinal arteries were slightly narrowed. The left border of cardiac dullness was at the midclavicular line; there were no murmurs. There was facial weakness on the lower left side and weakness of the left arm and leg. Ankle clonus and extensor plantar response were present on the left.

Roentgenograms of the skull were within normal limits. Lumbar puncture revealed bloody spinal fluid with an opening pressure equivalent to 260 mm. water. On the evening of admission a right carotid angiogram was performed which demonstrated a mass in the posterior parietal region; inferior to the mass there was evidence of a large arteriovenous malformation shunting blood into the deep venous circulation.

A craniotomy revealed an intracerebral hematoma at the base of which was a network of coiled arteries and veins. The hematoma was evacuated and the vessels coagulated. The blood pressure during surgery averaged 120/80 mm. Hg.

The postoperative course was marked by fever, restlessness and fluctuating levels of blood pressure, ranging from 128/64 to 240/120 mm. Hg. On the seventeenth postoperative day a second craniotomy was performed because of signs of increased intracranial pressure; another intracerebral hematoma was found at the same site and removed, but the patient died three hours after surgery.

At autopsy the heart weighed 410 gm. There were bilateral adrenal tumors, the left weighed 68 gm. and the right 58 gm. The microscopic diagnosis was pheochromocytoma. Assay for catecholamine revealed 5.5 mg. epinephrine per gm. of dry weight and 4.3 mg. norepinephrine per gm. of dry weight.

The thyroid gland appeared normal externally but on cut section there was a pale tan mass 2 cm. in diameter in the mid-portion of both the left and right lobes. The microscopic diagnosis was poorly differentiated, invasive, follicular adenocarcinoma of the thyroid. Only one parathyroid gland could be identified; it measured 0.9 by 0.6 cm., and the microscopic diagnosis was nodular enlargement (? adenoma) of parathyroid. The brain was the site of a massive

* From the Department of Medicine, State University of New York Upstate Medical Center and the Veterans Administration Hospital, Syracuse, New York.
† Present address: Department of Medicine, The Johns Hopkins Hospital, Baltimore, Maryland.

intracerebral and intraventricular hemorrhage involving the entire right cerebral hemisphere; cerebral edema was present. The pituitary gland appeared normal.

REVIEW OF CASES FROM THE LITERATURE

CASE II (Eisenberg and Wallerstein 1932 [*5*]). A sixty-three year old woman with a ten-year history of an enlarged thyroid gland and without known hypertension died. At autopsy bilateral pheochromocytomas were found, with metastases to bone, liver, lung, spleen and soft tissues. The thyroid gland was replaced by a large tumor mass, encapsulated, but with some invasion of the capsule. The microscopic diagnosis was papillary adenocarcinoma. No metastases were found.

CASE III (Beer, King and Prinzmetal 1937 [*6,7*]). At the age of seventeen this female had a thyroidectomy because of fatigue, throbbing headaches and sweating. The microscopic diagnosis was adenocarcinoma of the thyroid. (The slide was reviewed nine years later and the diagnosis was confirmed.) She continued to have symptoms and at the age of twenty-six a diagnosis of pheochromocytoma was made. Her blood pressure at this time was 280/200 mm. Hg. A pheochromocytoma of the left adrenal gland was removed at surgery. Her symptoms abated and her blood pressure fell to 110/70 mm. Hg.

CASE IV (Muntz, Ritchie and Gatch 1947 [*8*]). At the age of thirty-three this woman had a right hemithyroidectomy because of weakness and palpitations. The microscopic diagnosis was carcinoma of the thyroid. She died six years later. At autopsy bilateral pheochromocytomas were found, containing a total of 2,300 mg. of adrenalin. Also present was an adenocarcinoma in the left lobe of the thyroid and metastatic carcinoma from the thyroid in the cervical and paratracheal nodes.

CASE V (Freedman, Moulton, Rosenheim, Spencer and Willoughby 1958 [*9*]). A twenty-four year old woman had attacks of palpitations, weakness and headaches. A nodular goiter was partially removed in which a circumscribed tumor was present in each lobe; the microscopic diagnosis was anaplastic carcinoma. She received x-ray therapy and then a complete thyroidectomy was performed; carcinoma was again present in the specimen. Her blood pressure was as high as 240/150 mm. Hg at this time. The attacks of palpitation, weakness and headache became less frequent. At this time a clinical diagnosis of pheochromocytoma was made and at surgery a 115 gm. pheochromocytoma of the left adrenal gland was removed. The patient died, however, and at autopsy the right adrenal gland contained metastatic carcinoma of the thyroid.

CASE VI (Graeff, Muller and Moolenaar 1959 [*10*]). A thirty-seven year old woman had a five-year history of frequent attacks of dizziness and perspiration sometimes accompanied by headache and palpitations. Her blood pressure fluctuated to levels as high as 220/140 mm. Hg. There was a nodule in the left side of her neck. At surgery a pheochromocytoma of the right adrenal was removed. She remained hypertensive and died the day after surgery. At autopsy there was a pheochromocytoma of the left adrenal and several paragangliomata. In addition an anaplastic carcinoma of the thyroid was found with multiple small pulmonary metastases.

COMMENTS

By 1949 there were reports of 270 cases of pheochromocytoma in the literature [*11*]. During the following decade I was able to review reports of 267 additional cases, bringing the total number to 537. Autopsies were performed in 237 of these; information on the remaining 300 was obtained at surgery. Among the 537 cases of pheochromocytoma there were twenty-seven cases in which a malignant tumor of another organ was also present, an incidence of 5 per cent. Inasmuch as the incidence of malignancy for the general population at autopsy may be as high as 14 per cent [*12*], there would not appear to be an increased incidence of malignancy in pheochromocytoma.

The sites of the twenty-seven malignant tumors were as follows: carcinoma of the thyroid, six cases ([*5–10*] and present case); sarcoma, four cases [*13–16*]; carcinoma of the kidney, three cases [*17–19*]; carcinoma of the lung, two cases [*20,21*]; chronic myelogenous leukemia, two cases [*19,22*]; and one case each of multiple myeloma [*23*], malignant granulosa cell tumor of the ovary [*24*], neuroblastoma [*25*], carcinoma of the esophagus [*3*], colon [*19*], rectum [*26*], pancreas [*27*], prostate [*28*], breast [*29*], and cervix [*21*].

Three of the four cases of sarcoma occurred in patients with multiple neurofibromatosis, the tumors of which are well known to undergo sarcomatous degeneration. None of the other malignant tumors were more common than might be expected except carcinoma of the thyroid gland.

Carcinoma of the thyroid thus makes up 22 per cent of the malignancies in the 537 cases of pheochromocytoma, whereas the expected incidence of carcinoma of the thyroid is only 0.5 per cent of all cancers [*30*]. Although there is considerable controversy about the incidence of carcinoma of the thyroid in the general population, an autopsy incidence of 8 per 10,000 would

seem to be of the right order of magnitude [*30*]. The presence of carcinoma of the thyroid gland in six of the 537 cases of pheochromocytoma represents an incidence of 112 per 10,000; this is fourteen times the expected incidence.

An intriguing consideration is whether the hormones secreted by a pheochromocytoma may play a role in the development of thyroid carcinoma in some patients with pheochromocytoma. In experimental animals, administration of epinephrine has not been reported to cause carcinoma of the thyroid gland. It may result in hyperplastic changes in the thyroid, however [*31*]. The administration of epinephrine to animals results in a decrease in TSH secretion as reflected by a decrease in the radioactive iodine uptake of the thyroid and by a decrease in the release of radioactive iodine from the thyroid [*32*].

It is likely that the blood levels of catecholamines fluctuate considerably in patients with pheochromocytoma. When there are high levels of catecholamines in the blood, TSH secretion would decrease. The resulting low level of circulating thyroid hormone would act as a stimulus to increase the secretion of TSH. A subsequent increase in epinephrine would again depress TSH secretion. Over a period of years, what might be the effect of fluctuating levels of TSH on the thyroid gland?

It is possible to produce benign and malignant tumors of the thyroid in experimental animals by the prolonged administration of thiouracil, presumably by causing an increase in TSH secretion [*33,34*]. It is easier to produce tumors of the thyroid in animals by alternately giving thiouracil and iodine [*35*], i.e., alternately causing high and low levels of TSH. Thus it may follow that fluctuating levels of TSH brought about by epinephrine-producing tumors can, over a period of years, lead to the development of thyroid carcinoma in some patients.

SUMMARY

A case of pheochromocytoma associated with carcinoma of the thyroid gland is reported.

Among the 537 cases of pheochromocytoma in the literature, there are five other cases associated with carcinoma of the thyroid gland. Although the over-all incidence of malignancy of other organs is not increased in pheochromocytoma, the incidence of carcinoma of the thyroid gland is increased far beyond expectation based on chance concurrence.

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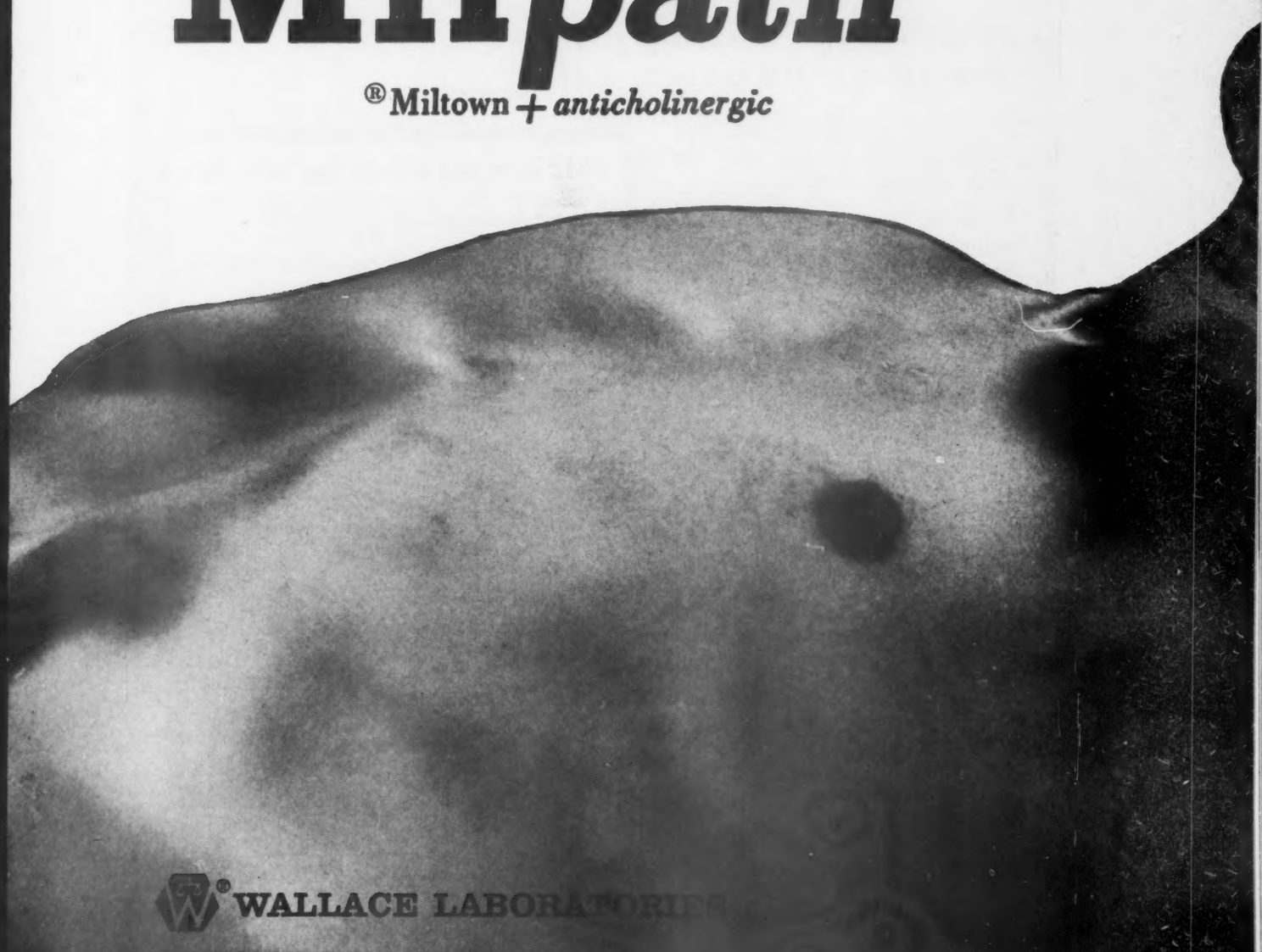

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Precautions — Side effects with Anadrol have been minimal when administered in the recommended daily dosage range. In those few instances where masculinizing effects have been noted in adults or children, reversal has been accomplished after discontinuing therapy.

Although Anadrol exhibits only a slight androgenicity, it shares with all androgens a tendency to favor sodium retention. For this reason, the drug should be used with caution in patients with heart disease.

Administration to children should not be continued beyond a 30-day period because of increased sensitivity to masculinizing agents. If such masculinizing symptoms develop, this drug should be discontinued.

Contraindications — Anadrol is contraindicated in the presence of carcinoma of the prostate and, because of changes which have been observed in hepatic function on long-term use with Anadrol at higher doses, it should be used with caution in patients with known hepatic damage. It is also contraindicated in nephritis and nephrosis.

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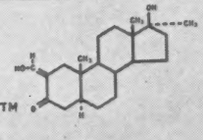

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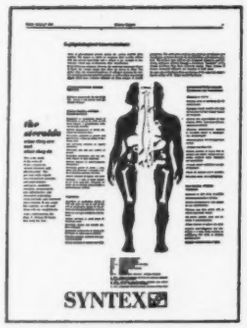

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INDICATIONS: Rheumatoid arthritis; other collagen diseases and related conditions; other musculoskeletal disorders (myositis, fibrositis, bursitis, etc.); allergic states, including chronic bronchial asthma and severe hay fever; and allergic/inflammatory diseases of the skin and eyes.

ADMINISTRATION AND DOSAGE: ATARAXOID dosage varies with individual response. Clinical experience suggests the following daily dosage: *Initial therapy*—4-6 **ATARAXOID** *5.0* Tablets. *Maintenance*—1-4 **ATARAXOID** *5.0* Tablets or 2-8 **ATARAXOID** *2.5* Tablets. After initial suppressive therapy, gradual reduction of prednisolone dosage should begin and continue until the smallest effective dose is reached. Prescribe in divided doses, after meals and at bedtime.

SIDE EFFECTS: Prednisolone may produce all of the side effects common to other corticosteroids. As with other corticosteroids, insomnia, mild hirsutism, moonface and sodium retention have occurred. Osteoporosis may develop after long-term corticosteroid therapy.

PRECAUTIONS AND CONTRAINDICATIONS: Usual corticosteroid precautions should be observed. Incidence of peptic ulcer may increase on long-term prednisolone therapy. However, therapy has often been maintained for long periods without adverse effects. Contraindicated in infectious disease including active tuberculosis (except under close supervision), peptic ulcer, certain infections of the cornea, such as dendritic keratitis, superficial punctate keratitis, epidemic keratoconjunctivitis, and in patients with emotional instability. Caution is indicated in the treatment of diabetic patients and patients with severe cardiovascular disease, and in some cases sodium restriction and potassium supplementation must be considered.

SUPPLIED: As green, scored **ATARAXOID** *5.0* Tablets, containing 5 mg. prednisolone and 10 mg. hydroxyzine hydrochloride and blue, scored **ATARAXOID** *2.5* Tablets, containing 2.5 mg. prednisolone and 10 mg. hydroxyzine hydrochloride.

More detailed professional information available on request.

*Warter, P. J.: Prednisolone-hydroxyzine combination in rheumatoid arthritis, J. M. Soc. New Jersey 54:7, 1957.

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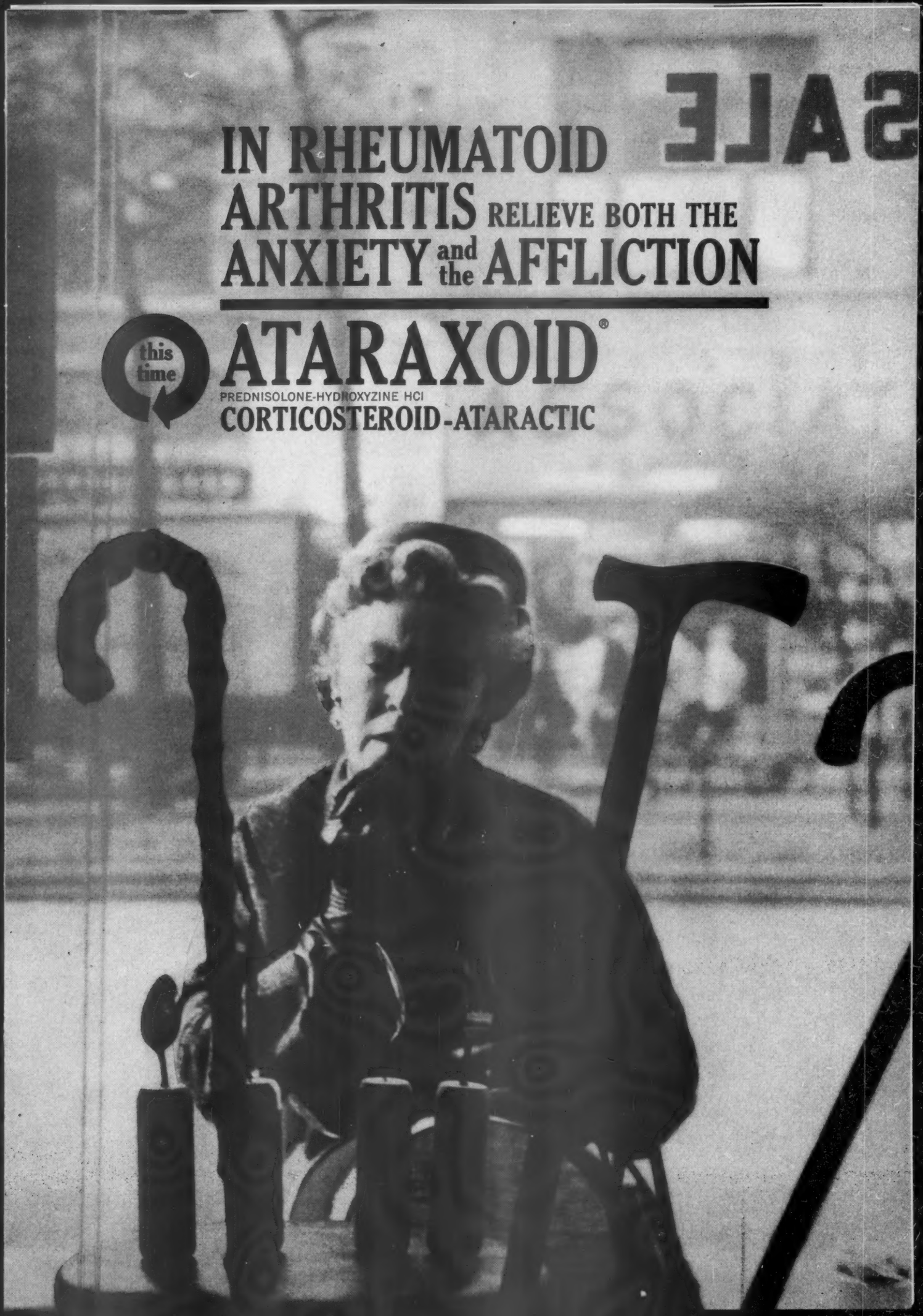
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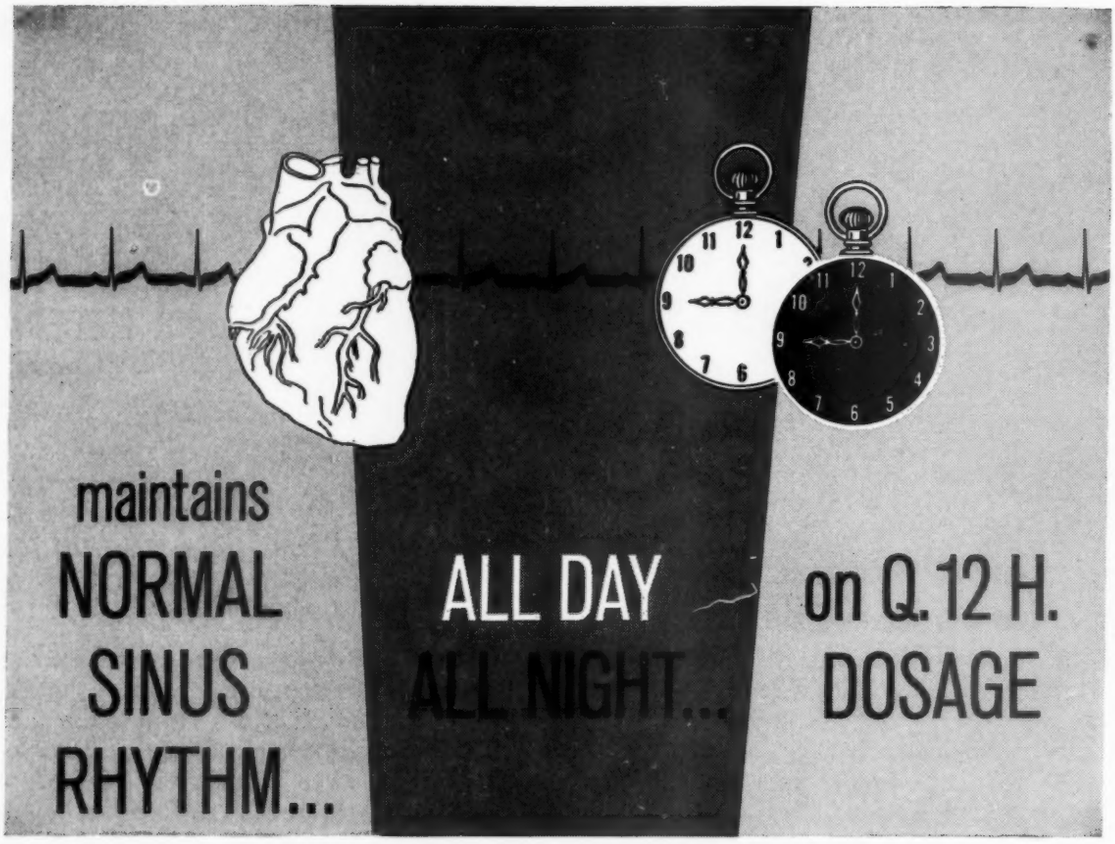

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METRECAL™ AND OBESITY

A DISCUSSION: PART II

the second of two parts of a discussion on the significance
of Metrecal in the management of obesity

"Persons who are naturally very fat are apt to die earlier than those who are slender."
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METRECAL*: PRINCIPLE AND METHOD

Metrecal brand dietary for weight control embodies two principles: (1) a complete break from the individual's usual eating habits long enough to achieve the desired weight loss and to adjust to lower caloric intake through the judicious use of proper amounts and combinations of usual foods, and (2) a single food adequate in nutrition and prepackaged to supply a measured number of calories for ingestion during one day.

These principles drive directly at the immediate cause of obesity: the *habit* of *overeating*. As with other harmful habits, a complete break in the established cycle of stimulus and response is usually essential.

Persons susceptible to obesity are prone to justify their condition, and are quite candid about their inability or unwillingness to establish control of the habit of overeating. For example, a carefully controlled study[1] of *those who consider themselves overweight* gave this picture:

"I eat more than usual when I am nervous or anxious." (63%)
"Eating is one of my greatest pleasures." (71%)
Small wonder, therefore, that they also say, *"I find it hard to stay on a diet." (65%)*

In view of these facts, it is not surprising that the rate of failure noted by physicians is as high as 80% for patients undergoing treatment for obesity.[2,3]

The reasons behind the habit of overeating may vary widely: cultural patterns of many regional and ethnic groups,[4] personal uncertainty and insecurity seeking gratification,[4,5,6] sedentary lives for much of the adult population,[7,8] and the beckoning abundance of an affluent economy.[9]

These factors may explain, but they do not justify obesity, which seriously shortens life expectancy,[10] aggravates other diseases,[11,12] increases anesthetic and other hazards during surgery,[13-16] and increases susceptibility to illness.[15,16,17] Where virtually half of the adult population is above the level of desirable weight,[18] the extent and seriousness of the problem are evident.

The simple admonition to eat less and to eat more wisely states a principle but fails to suggest a practical method for achieving this goal. In most situations the methods usually applied have been complicated, ineffective or undependable.

One may conclude that the persistence and prevalence of obesity have been due to the lack of an effective means to make a complete break from the habit of overeating.

The use of Metrecal dietary has led to successful weight reduction and control because the principle of the complete break has been embodied in one product, which is: *simple; effective; dependable.*

Clinical experience to date will be related to each of these characteristics in the sections that follow.

*Metrecal is Mead Johnson & Company's trademark for dietary for weight control.

EFFECTIVENESS FOR WEIGHT LOSS

Thousands of patients have found Metrecal effective for losing weight. Three clinical studies on the effectiveness of Metrecal for weight loss, reported in the medical literature, are summarized below. Twenty-two additional studies are in progress under medical supervision. Many of these will soon be reported.

Dr. R. J. Antos[19] reported studies on 100 overweight patients during a 12-day period in which their only food intake was Metrecal (in an amount supplying 900 calories daily), lettuce, celery, and noncaloric beverages. The average weight loss was:

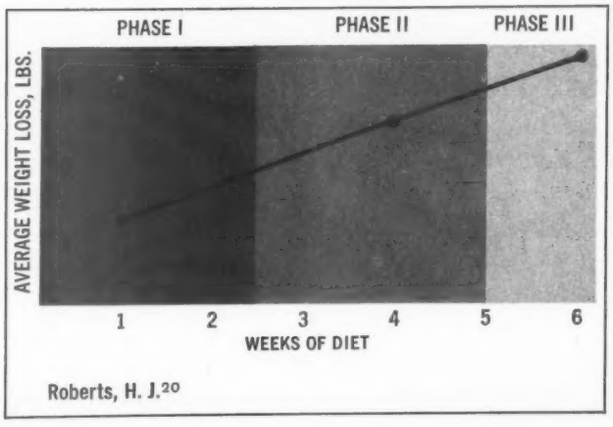
Weight Loss in 12 days	*lbs.*
Men (14)	8.2
Women (86)	6.3
Average for Men and Women (100)	6.5

The ingestion of only 900 calories daily (a change from their usual habit of overeating) was the basis for this successful weight loss.

Dr. H. J. Roberts[20] reported observations on 57 patients: some with serious and progressive medical disorders, some requiring future surgery, and others who had become discouraged after a number of futile attempts to reduce. He divided his treatment regimen into three phases: Phase I (Metrecal alone) lasted from 5 days to 5 weeks, Phase II (a low-calorie diet consisting in part of Metrecal and in part of usual foods) until desired weight loss was achieved, and Phase III during which the patient was returned to a diet of limited but usual foods.

Weight loss averaged 16 pounds in 6 weeks, as shown in the following chart:

AVERAGE WEIGHT LOSS OF PATIENTS ON 3-PHASE METRECAL DIET



Roberts, H. J.[20]

In addition to the weight loss, many of these medical and surgical patients experienced clinical improvement and no metabolic crises were precipitated.

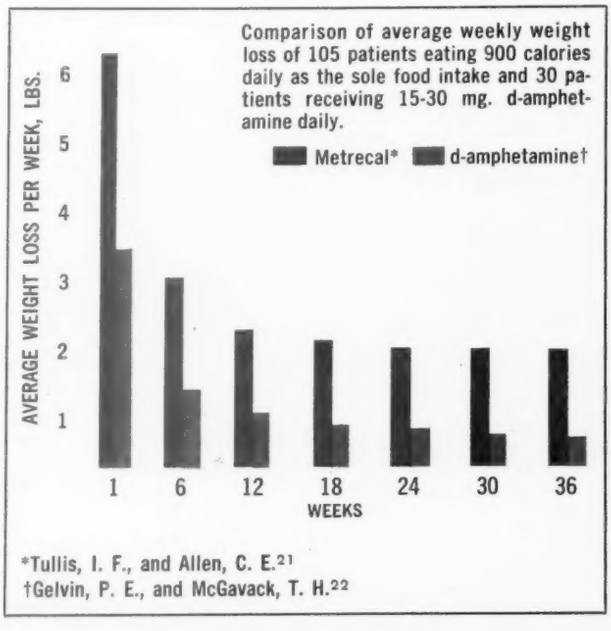
Drs. I. F. Tullis and C. E. Allen[21] reported studies on 105 overweight persons, 25 men and 80 women. All (except one on the metabolic ward) were treated as outpatients with Metrecal (8 oz. Powder) as the sole daily diet. Eighty per cent of the subjects were more than 30% overweight. They came from all walks of life: professional; sedentary and manual workers; skilled and unskilled. Examination revealed a wide variety of physical aberrations: coronary, gastrointestinal, and metabolic diseases.

During the first few days on the Metrecal regimen some malaise, fatigue and irritability were reported. After this initial "hump" was passed, the appetites of most patients were satisfied, and they felt exceptionally well.

The *length of time* during which these patients were maintained on the 900-calorie Metrecal diet is instructive. Twenty-five of the patients were on the diet for 16 weeks, and eight patients for 26 weeks. No significant adverse reactions were observed.

The successful weight loss of these patients is graphically presented in the following chart:

COMPARATIVE WEIGHT LOSS OBSERVED WITH METRECAL AND d-AMPHETAMINE

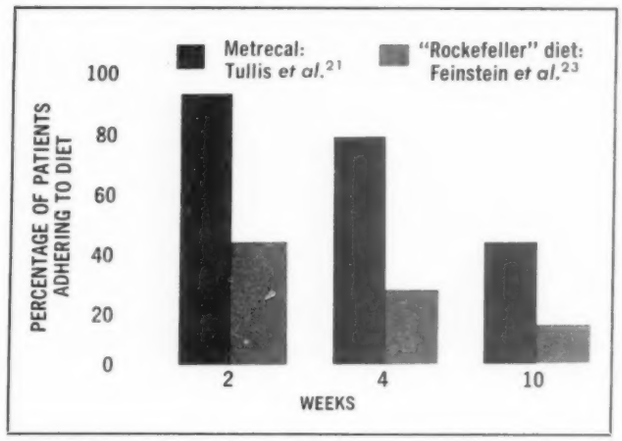


*Tullis, I. F., and Allen, C. E.[21]
†Gelvin, P. E., and McGavack, T. H.[22]

It is seen that weight loss the first week is greater than during subsequent weeks. As the diet is prolonged, weight loss stabilizes at about two pounds per week. The chart also compares this weight loss with that of patients (reported in the classic studies of Gelvin and McGavack[22]) ingesting d-amphetamine to control appetite.[22] These data show that, with time, the effectiveness of d-amphetamine decreases markedly so that weight loss per week becomes negligible.

It has been noted that patients adhered to the Metrecal regimen exceptionally well. Since adherence to a diet is critically important in achieving weight loss, it is of interest to compare adherence to Metrecal with that reported by Feinstein *et al.*[23] in their pioneering study of a reducing diet of 900 calories. This is shown in the accompanying chart:

COMPARISON OF STRICT ADHERENCE TO "ROCKEFELLER" DIET AND TO METRECAL AS SOLE FOOD INTAKE



The difference between adherence to the two diets is obvious.

RECORD OF DEPENDABILITY AND SAFETY

The nutritional adequacy, dependability and uniformity of Metrecal brand dietary for weight control were documented in Part I of this Discussion, previously published in this Journal. The composition, nutritional adequacy and caloric distribution of Metrecal were presented in graphic form. Similarly, its vitamin, mineral, protein, amino acid and fatty acid contents were described in diagram.

Experimental animals (the standard tool used to determine nutritional adequacy) grew to maturity, reproduced, and successfully raised their young, when fed Metrecal as the sole diet.[1] Thus, there is direct laboratory confirmation of the correctness of its nutritional formulation and its suitability for long-term administration.

Clinical studies summarized in the preceding section have likewise demonstrated safety. No adverse effects were noted in patients (1) with a wide variety of disorders, or (2) who limited their food intake to Metrecal for 1 to 26 weeks.

The most rigorous test of safety, however, is the long-term use of Metrecal as the sole source of nutrition. In the report by Tullis, Allen, and Overman,[21] one patient initially weighing 473½ pounds lost 217 pounds in *62 weeks* on Metrecal alone. She has since continued her reducing program with Metrecal as the only food for a total of *116 weeks*.[1] Another patient reduced from 230 pounds to 133 pounds in *52 weeks*. During this period[1] she underwent six weeks of hospitalization for injuries received in an automobile accident, in which she suffered fractured ribs and multiple contusions complicated by thrombophlebitis of one extremity. The Metrecal diet was continued during recovery and all injuries healed in the expected time and manner.

The formulation of Metrecal brand dietary for weight control assures an adequacy of vitamin and mineral intakes consistent with long-term use and safety. The protein level is adequate for maintenance of muscular tissue (prevention of nitrogen wastage) and the avoidance of hypoproteinemia.[24,26]

In some patients minimal side reactions have been observed. In part these relate to the absence of bulk in Metrecal. When constipation occurs, it may be relieved by ingestion of low-caloric, high-bulk substances, such as celery, carrots or lettuce, as suggested in the leaflet accompanying each can of Metrecal.

Other patients have at times complained of flatulence. The solution to this problem may reside in resourceful experimentation with customary measures, dietary adjustments or other procedures deemed suitable by the physician.

At the beginning of a diet restricted to 900 calories of Metrecal, some patients experience varying degrees of weakness or lassitude. This phase is soon passed and a feeling of well-being frequently ensues as the diet is continued.

APPLICATION AND ADVANTAGES

The principles on which Metrecal brand dietary for weight control is based were stated at the beginning of this discussion: a break in dietary food habit until weight loss has been achieved and readjustment to a lower caloric intake of usual foods attained; and a nutritionally complete food, prepackaged to supply the proper number of calories for one day's total food. These principles have been applied most perceptively by Roberts,[20] who defined three steps to be followed in losing weight and re-educating the patient to a proper food level as follows:

Phase I. Metrecal alone.
A diet of Metrecal (900 calories per day) as the only food, continuing for from 5 days to 5 weeks.

Phase II. Metrecal alternating with diet.
A low-calorie diet consisting of one or two meals as Metrecal (225 calories each) and a third meal of usual foods in moderate amount, continued till desired weight loss is achieved.

Phase III. Diet alone.
A gradual return to a diet of usual foods, in the quantities necessary to avoid regaining weight and to hold weight at the achieved level.

From observations made during the successful application of this program, Roberts[20] outlined the advantages of Metrecal. These are summarized as follows:

1. It eliminates the guesswork and inconvenience of calorie counting.

2. It keeps the patient away from the table and reduces temptation during the critical initial phase.

3. It satisfies the appetite in the majority of patients.

4. It obviates the problem of making decisions in the choice and amount of foods.

5. It does not cause negative nitrogen balance.

6. It is highly practical, and there is no mixing a number of ingredients.

7. It can be employed either as the sole source of nutrition, or it can be used in a flexible manner in coordination with a hypocaloric diet.

8. It is effective in satisfying appetite and in weight reduction in cooperative patients.

9. It gives the patient a definite time in which a reasonable weight reduction can be expected, whereas a 1200- to 1800-calorie diet may entail several months of rigorous food restriction.

10. The 3-phase dietary regimen gives the physician several weeks to instruct the patient concerning proper diet and to return to usual foods in limited amount.

11. It virtually frees both the physician and the patient from dependence on the anorexigenic drugs, metabolic stimulants and the hydrophilic colloids.

12. It has been used without apparent detriment in a panorama of medical disorders.

Regarding the particular qualities of Metrecal that aid in its successful use, Tullis and Allen[21] comment as follows:

"The simplicity, convenience, and accuracy of the formula contributed significantly to the success of the regimen. No diet lists were necessary; no tables of caloric values were used; no opportunities arose for errors in estimating caloric intake; no special substitute recipes were needed, and deviations from the diet could not easily be rationalized by the patient."

The convenience and dependability of Metrecal are cogently stated by Wilson:[25]

"For the first time the physician could look a fat patient in the eye and say, 'Stop eating.' He could tell his patient to take 900 calories, no more and no less, every day for the next seven days and could predict the weight loss in advance. There was nothing fuzzy about that kind of prescription. Patients liked it; doctors liked it."

CONCLUSION

This 2-part Discussion of Metrecal[T.M.] and Obesity has outlined:

1. *Simple facts about obesity.*
2. *The chemical and biological qualities of Metrecal.*
3. *Clinical data that support its value and effectiveness.*
4. *Its dependability and safety.*

Metrecal brand dietary for weight control is an effective and practical product with which to attack the problem of obesity. As such, it is an important tool for the physician; and, one may hope, can reduce significantly the incidence of obesity.

At present, 22 studies in eleven institutions are under way to extend our knowledge of the usefulness of Metrecal in the treatment of obesity as related to specific diseases. The results of these studies will be reported from time to time.

Unlike the host of diet fads, short-lived crash programs, and bizarre preparations, Metrecal was designed by scientists for use in a rational system of weight loss and control. With continuing clinical study and medical approbation, its value should remain undiminished for years to come.

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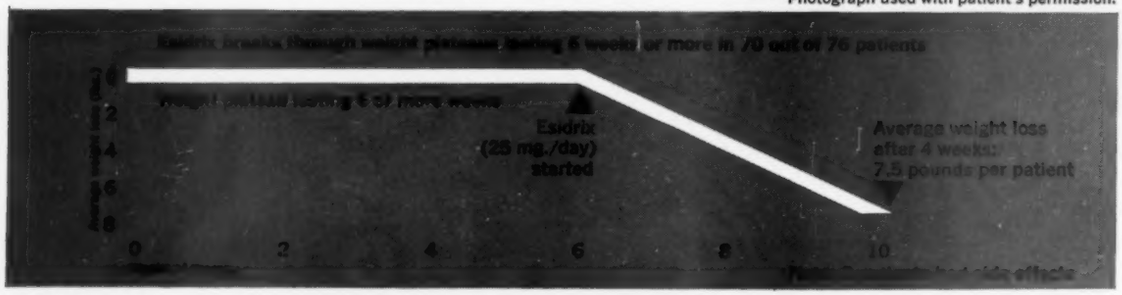
Weight problem? Start the reducing program right, keep it going right with Esidrix® Esidrix-K®

Recent studies show that the diuretic action of Esidrix improves results of weight-reducing programs 2 ways:

1. As an adjuvant in initiating treatment: Esidrix induces greater weight losses in the first few days than a conventional regimen.[1] This weight loss may be significant in itself (depending on the degree of fluid retention). But more than that, the quick loss of even a few pounds builds confidence in the weight-reducing program, inspires determination to follow it faithfully.

2. As an adjuvant in maintenance treatment: Esidrix eliminates retained water—with consequent weight losses—to break through the weight plateaus so often encountered in antiobesity programs. (See schematic graph below.) The new weight loss cheers the patient and helps overcome his tendency to eat too much.

Photograph used with patient's permission.


Esidrix breaks through weight plateaus lasting 6 weeks or more in 70 out of 76 patients
Esidrix (25 mg./day) started
Average weight loss after 4 weeks: 7.5 pounds per patient
0
2
4
6
8
10

(Adapted from Einhorn and Kalb[2])

Esidrix®
(hydrochlorothiazide CIBA)

For complete information about Esidrix and Esidrix-K (including dosage, side effects, and cautions), see Physicians' Desk Reference, or write CIBA, Summit, N. J.

References: 1. Ray, R. E.: To be published. 2. Einhorn, H. P., and Kalb, S. W.: Clin. Med. 7:1995 (Oct.) 1960.

Supplied: ESIDRIX Tablets, 25 mg. (pink, scored) and 50 mg. (yellow, scored). ESIDRIX-K Tablets 25/500 (white, coated), each containing 25 mg. Esidrix and 500 mg. potassium chloride. **NEW STRENGTH ESIDRIX-K NOW AVAILABLE:** ESIDRIX-K Tablets 50/1000 (white, coated), each containing 50 mg. Esidrix and 1000 mg. potassium chloride.

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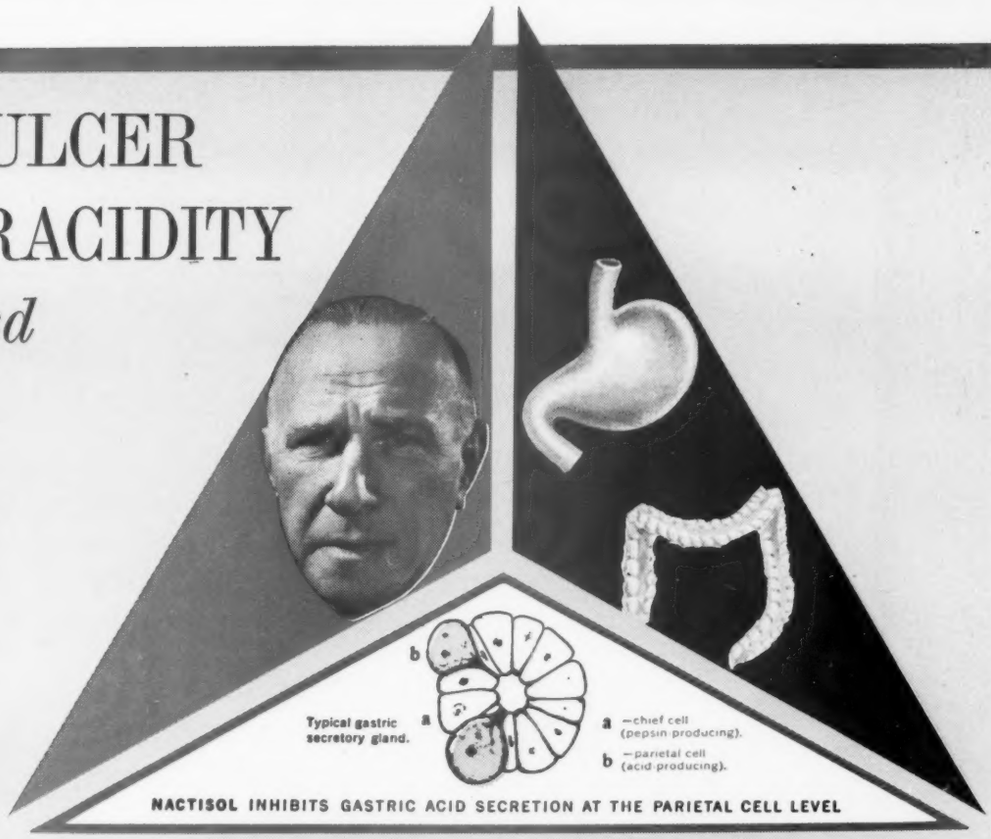
IN PEPTIC ULCER AND HYPERACIDITY *with associated* tension and nervousness


Typical gastric secretory gland.
a —chief cell (pepsin-producing).
b —parietal cell (acid-producing).
NACTISOL INHIBITS GASTRIC ACID SECRETION AT THE PARIETAL CELL LEVEL

NACTISOL*

- suppresses gastric acid secretion at the parietal cell level
- decreases gastrointestinal hypermotility
- relieves nervousness and tension

NACTISOL combines:

NACTON® 4 mg. (poldine methylsulfate†) — new inhibitor of gastric acid secretion and hypermotility "...reduces the total output of gastric HCl by about 60%"[1]

plus

BUTISOL SODIUM® 15 mg. (butabarbital sodium) — "daytime sedative" with highest therapeutic index[2] (highly effective, minimal side effects)

smooth, predictable sedation of *6 hours' duration*

- Side effects with NACTISOL therapy have been minimal.[3-5]

NACTISOL*...in scored, yellow tablets

References

1. Douthwaite, A. H.: The Development of the Treatment of Duodenal Ulcer, Proc. Roy. Soc. Med. *51*:1063-1068 (December) 1958. 2. Batterman, R. C., Grossman, A. J., Leifer, P., and Mouratoff, G. J.: Clinical Re-evaluation of Daytime Sedatives, Postgrad. Med. *26*:502-509 (October) 1959. 3. Steigmann, F.: Clinical Report to McNeil Laboratories. 4. Lorber, S. H.: Clinical Report to McNeil Laboratories, December 6, 1960. 5. Rider, J. A.: Clinical Report to McNeil Laboratories.

McNEIL McNEIL LABORATORIES, INC., Fort Washington, Pa.

*Trademark
†U. S. Patent

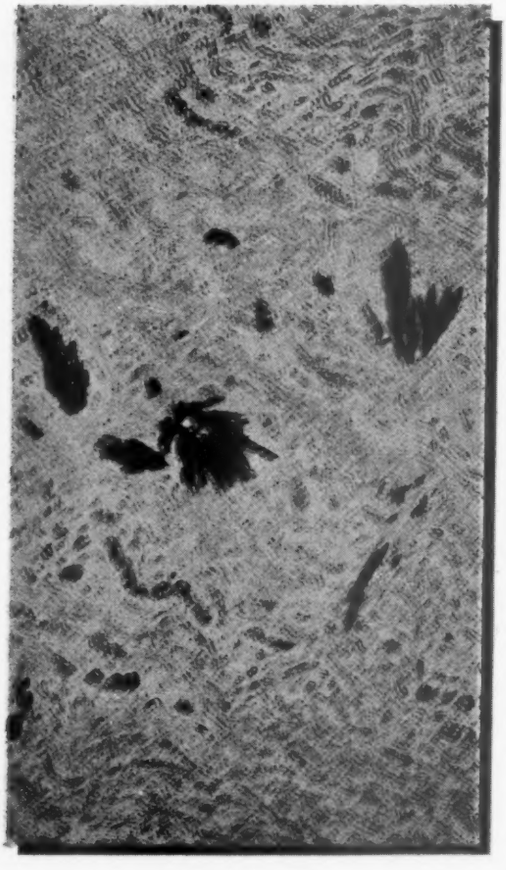
GOUT

"For centuries the victims of gout have been the subject of lampoons and caricatures. We now know that they should rather be the objects of great concern, for the disease is painful, disabling and is accompanied by complications that impair health and shorten life."[1]

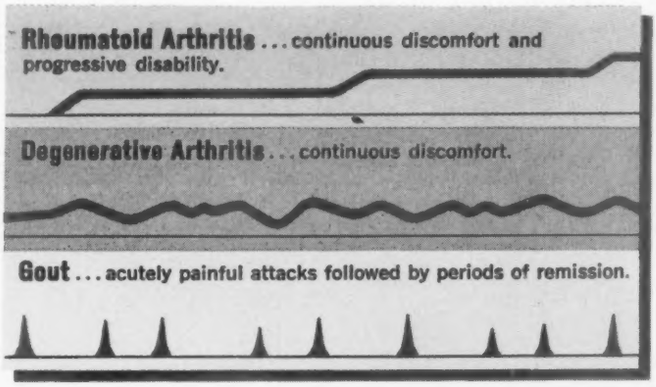
Kidney impairment, with varying degrees of hypertension and arteriosclerosis, is the critical complication of gout. "From 30 to 50 per cent of gouty patients are said to die of renal disease."[2]

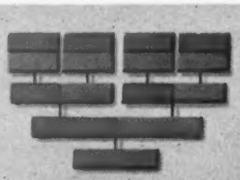
Tophus in the calyx, surrounded by fibrinoid exudate and detached mucosal epithelium.[3]

The mid- and outer portion of the pyramid with typical uric acid crystals in the collecting system.[3]



AIDS TO DIAGNOSIS


Rheumatoid Arthritis ... continuous discomfort and progressive disability.
Degenerative Arthritis ... continuous discomfort.
Gout ... acutely painful attacks followed by periods of remission.



"If a family history of gout is obtained, even though it is one or two generations removed, this information is significant."[4]

"The metatarsophalangeal joint of a great toe is affected early or repeatedly in some cases, rarely or never in others."[6]

"All patients complaining of non-traumatic musculoskeletal discomfort should have at least one serum uric acid determination."[5]

Colchicine test: "Colchicine should be administered as early as possible after the onset of articular distress, 1 mg. ... every 2 hours until the onset of gastro-intestinal distress. From 5 to 8 mg. usually are required."[9] Pain relief is highly indicative of gout.

THE "INSULIN OF GOUT"[7]

"Of the various drugs with uricosuric activity, probenecid [BENEMID] has proved most desirable for long-term administration."[8]

BENEMID®

PROBENECID

Therapy with BENEMID should be continued without interruption since hyperuricemia recurs when dosage is terminated. The rare patient who experiences gastric discomfort is usually benefited by decreasing the dosage. Dosage: 0.25 Gm. twice daily for one week, followed by 1 Gm. daily in divided doses. Supply: 0.5 Gm. tablets.

A COMPLEMENTARY FORMULATION OF TWO CLASSIC ANTI-GOUT AGENTS

"... the greater the experience we have with the combination of colchicine and Benemid the greater the reliance we place upon these two drugs."[9]

ColBENEMID®

COLCHICINE WITH BENEMID

Dosage: One tablet daily for one week, followed by one tablet twice daily. Supply: Each tablet contains 0.5 mg. colchicine and 0.5 Gm. BENEMID. Bottles of 100 and 1000.

1. Cornish, A. L.: J. Kentucky M.A. 58:707, June, 1960. 2. Wyngaarden, J. B.: Arthritis & Rheumatism 1:191, June, 1958. 3. Talbott, J. H. and Terplan, K. L.: Medicine 39:405, Dec., 1960. 4. Talbott, J. H.: Gout, New York, Grune & Stratton, 1957, p. 123. 5. Kuzell, W. C., et al.: J. Chron. Dis. 2:645, Nov., 1955. 6. Hench, P. S.: Gout and gouty arthritis, in Cecil, R. L.: A textbook of medicine, ed. 10, Phila., W. B. Saunders Co., 1959. 7. Bartels, E. C., and Kepkay, P. H.: Bull. Vancouver M.A. 29:306, April, 1953. 8. Boland, E. W.: World-Wide Abstracts of Gen. Med. 3:16, Jan., 1960. 9. Talbott, J. H.: Current Med. Dig. 26:57, Nov., 1959.

Before prescribing or administering BENEMID or ColBENEMID, the physician should consult the detailed information on use accompanying the package or available on request.

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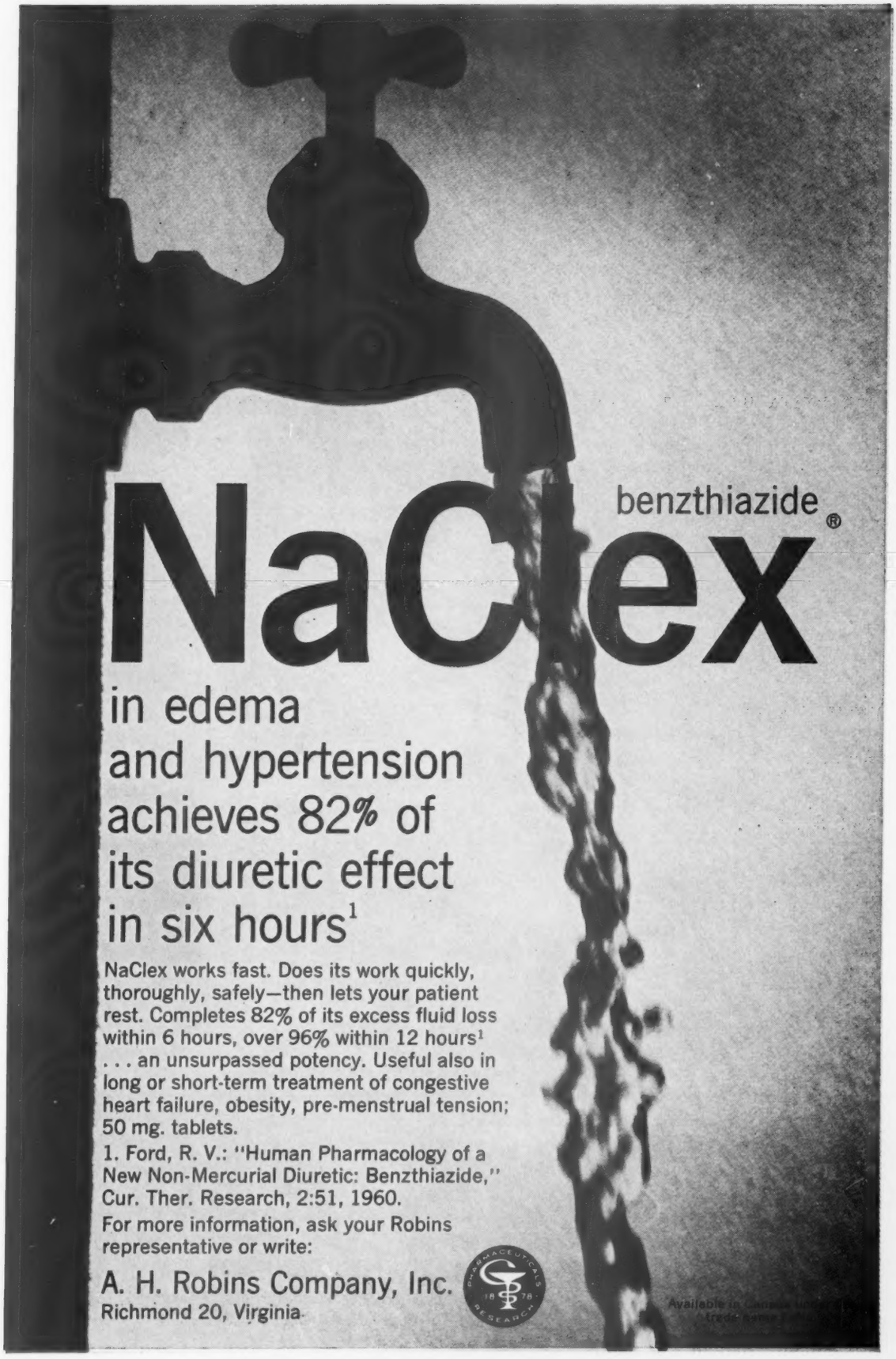
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in edema
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achieves 82% of
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1. Ford, R. V.: "Human Pharmacology of a New Non-Mercurial Diuretic: Benzthiazide," Cur. Ther. Research, 2:51, 1960.
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restores
the will
to
improve

In Brief Niamid, brand of nialamide, is 1-(2-[benzylcarbamyl] ethyl)-2-isonicotinyl-hydrazine, a well-tolerated antidepressant that may correct or relieve depression on once-a-day dosage. **Indications:** Depressive syndromes of varying degrees of severity may be responsive to Niamid including: involutional melancholia, postpartum depression, depressed phase of manic-depressive reaction, senile depression, reactive depression, schizophrenic reaction with depressive component, psychoneurotic depression. ■ In neurotic or psychotic patients, Niamid may normalize or favorably modify aberrant or excessive reactions and symptoms of depression such as: phobias, guilt feelings, dejection, feeling of inadequacy, discouragement, worry, uneasiness, distrustfulness, hypochondriacal and nihilistic ideas, difficulty in concentration, insomnia, loss of energy or drive, indecision, hopelessness, helplessness, decreased functional activity, emotional and physical fatigue, irritableness, inability to rest or relax, sadness, anorexia and weight loss, and withdrawal from society. *In the withdrawn patient,* Niamid may elevate the mood so that there is increased activity, increased awareness and interest in surroundings, and increased participation in group activities. Appetite may be increased and there may be decreased fatigability. Lack of clinical response to other antidepressant therapy does not preclude a favorable response to Niamid. Relief of depression may also be evidenced by elimination or reduction of the need for somatic therapy, such as electroshock. *In patients suffering from depression associated with chronic illness,* Niamid may improve mental outlook, reduce the impact of pain, decrease the amounts of narcotics or analgesics needed, and improve appetite and well-being. *In patients with angina pectoris,* Niamid has been found to be a useful adjunct to management through reduction in frequency of attacks and pain. **Dosage:** Starting dosage is 75 to 100 mg. on a once-a-day or divided daily basis. This may subsequently be adjusted depending upon the tolerance and response. Responses to Niamid are not usually rapid, and revisions of dose should be withheld until at least a few days have elapsed at each level. Increments or decrements of 12½-25 mg. are generally sufficient. A daily dosage of 200 mg. is the maximum recommended for routine use. (As much as 450 mg. daily has been used in some patients.) **Side Effects:** Niamid, in clinical use, has been characterized by a significant lack of toxicity. It is generally well tolerated. Nervousness, restlessness, insomnia, hypomania, or mania, sometimes occur. Occasional headache, weakness, lethargy, vertigo, dryness of the mouth, blurred vision, increased perspiration, constipation, mild skin rash, mild leukopenia, and epigastric distress may be obviated or modified by reductions in dose. Effects due to monoamine oxidase inhibition persist for a substantial period following discontinuation of the drug. **Precautions and Contraindications:** Hepatic toxicity has not been reported in extensive clinical studies. However, if previous or concurrent liver disease is suspected, the possibility of hepatic reactions and liver function studies should be considered. ■ The suicidal patient is always in danger, and great care must be exercised to maintain all security precautions. The apathetic patient may obtain sufficient energy to harm himself before his depression has been fully alleviated. ■ Niamid may potentiate sedatives, narcotics, hypnotics, analgesics, muscle relaxants, sympathomimetic agents, thiazide compounds and stimulants, including alcohol. Caution should be exercised when rauwolfia compounds and Niamid are administered simultaneously. Rare instances have been reported of reactions (including atropine-like effects, and muscular rigidity) occurring when imipramine was administered during or shortly after treatment with certain other drugs that inhibit monoamine oxidase. **In Cardiology:** The central effects of Niamid may encourage hyperactivity and the patient should be closely observed for any such manifestation. Orthostatic hypotension or hypertensive episodes occur in a few individuals; cardiac patients should be carefully selected and closely supervised. **In Epilepsy:** Although in some patients therapeutic benefits have been achieved with Niamid, in others the disease has been aggravated. Care should be exercised in the concomitant use of imipramine, since such treatment with monoamine oxidase inhibitors has been reported to aggravate the grand mal seizures. **In Tuberculosis:** Existing data do not indicate whether resistance of M. tuberculosis to isoniazid may be induced with Niamid therapy; nevertheless, it should be withheld in the depressed patient with coexisting tuberculosis who may need isoniazid. ■ As with all therapeutic agents excreted in part via the kidney, due caution in adjusting dosage in patients with impaired renal function should be observed. **Supplied:** Niamid (Nialamide) Tablets, 25 mg.: 100's—pink, scored tablets; 100 mg.: 100's—orange, scored tablets./*More detailed professional information available on request.*

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you "reach"
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in any rheumatic 'itis'

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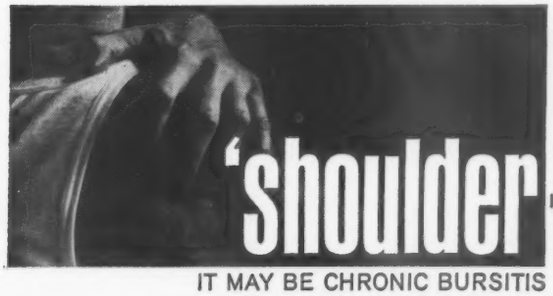
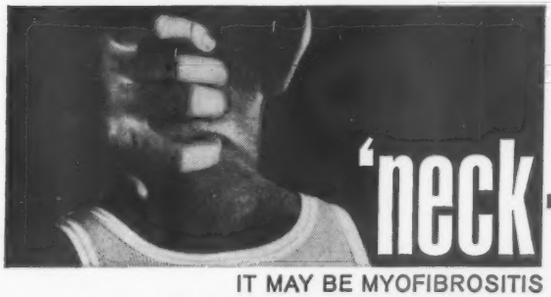


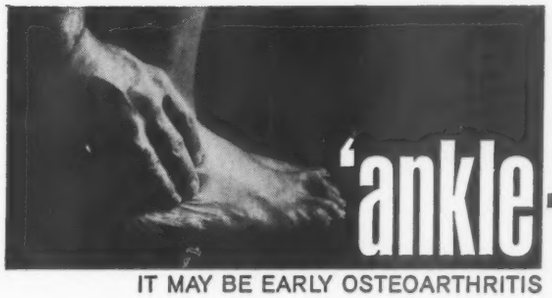
'shoulder-itis'

IT MAY BE CHRONIC BURSITIS



'neck-itis'

IT MAY BE MYOFIBROSITIS



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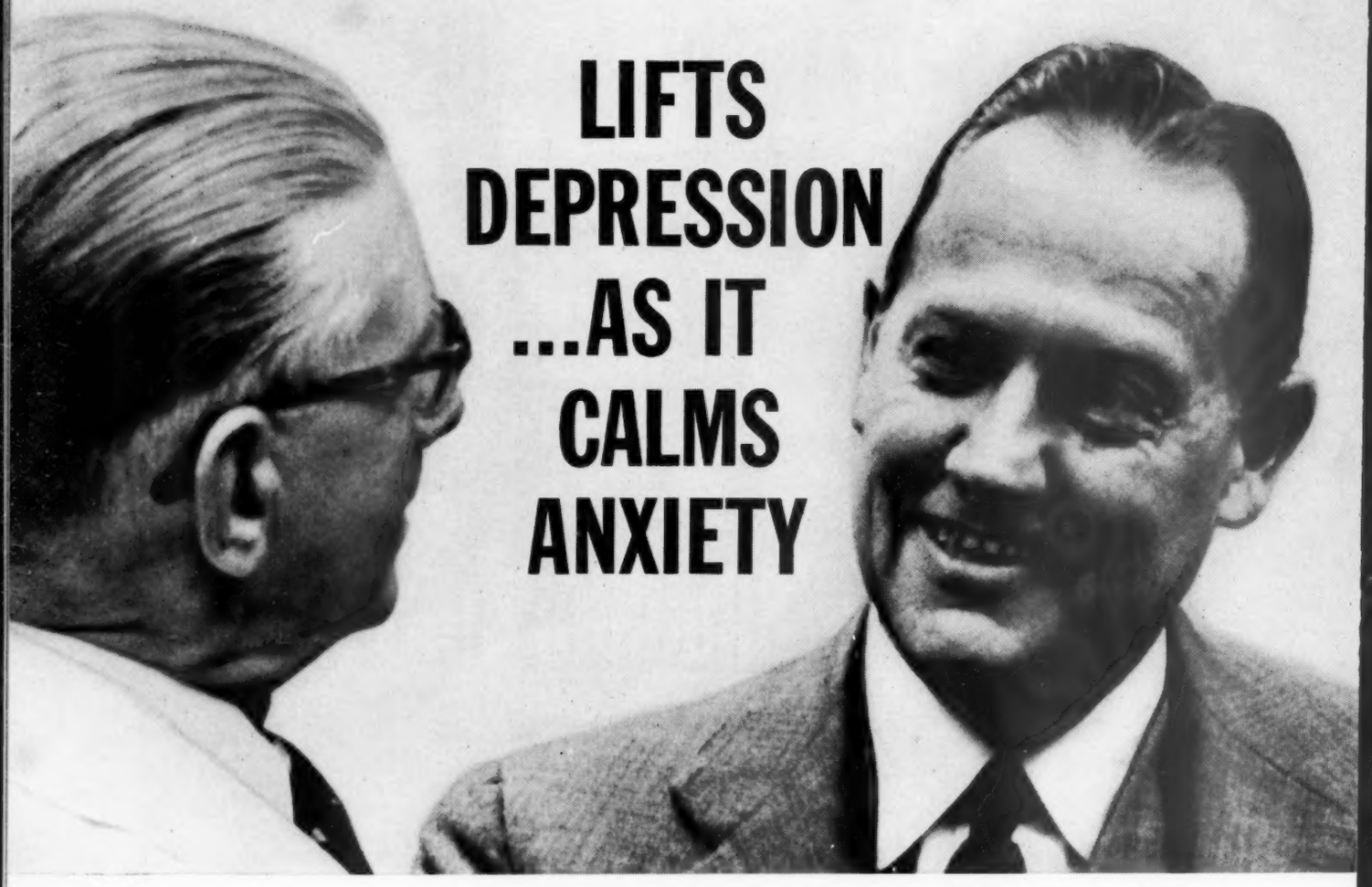

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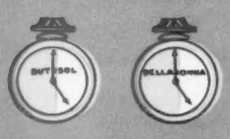

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IN BRIEF

INGREDIENTS: Each Urobiotic capsule contains 125 mg. Terramycin® (oxytetracycline) with 125 mg. glucosamine HCl, 250 mg. sulfamethizole, and 50 mg. phenylazo-diamino-pyridine HCl.

INDICATIONS: Urobiotic is indicated in the treatment of a number of common genitourinary infections caused by susceptible organisms. It may also be used prophylactically before and after genitourinary or pelvic surgery, following instrumentation procedures, during the use of retention catheters, and in patients with conditions such as cord bladder or cystocele.

DOSAGE: In adults, a dose of 1 or 2 capsules four times daily is suggested, depending upon the severity and response of the infection. In children 60 to 100 lbs., the suggested average dose is 1 capsule four times daily; in children under 60 lbs., 1 capsule three times daily. Therapy should be continued for a minimum of 7 days or until bacteriologic cure is effected in acute urinary tract infections.

CONTRAINDICATIONS: Urobiotic may be contraindicated in patients with chronic glomerulonephritis, hepatitis, hepatic failure, uremia, and obstructive lesions of the urinary tract, and should not be used in patients sensitive to any of its components.

PRECAUTIONS: The use of broad-spectrum antibiotics may, in rare cases, result in an overgrowth of nonsusceptible organisms, such as monilia or staphylococci. Should such superinfection occur, therapy with Urobiotic should be discontinued and specific therapy instituted as shown by susceptibility testing. The use of sulfonamides may cause renal crystalluria or skin rash, as well as other toxic or sensitivity reactions. If any of these occur, discontinue use.

SUPPLIED: Urobiotic capsules, yellow-and-grey, bottles of 50.

Pfizer

More detailed professional information available on request.

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orphenadrine citrate 100 mg. tablets

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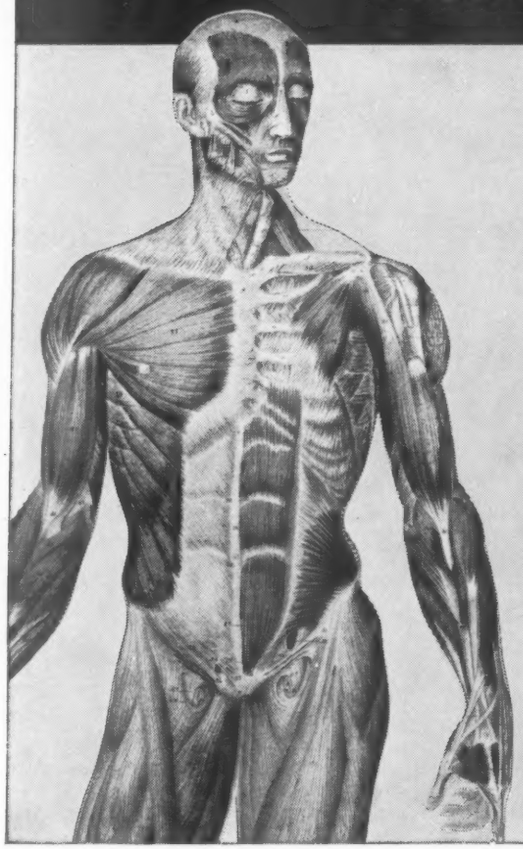
relieves the pain...

restores normal function



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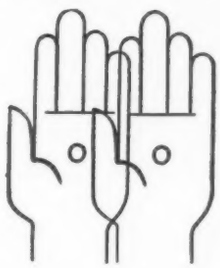
Simple dosage



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SUPPLIED: *Tablets*, 1 mg. (pale orange, scored). *Lontabs*, 2.5 mg. (orange). *Syrup* (pink), containing 1 mg. Forhistal maleate per 5-ml. teaspoon. *Pediatric Drops* (pink), containing 0.5 mg. Forhistal maleate per 0.6 ml.

For complete information about Forhistal (including dosage, cautions, and side effects), see Physicians' Desk Reference or write CIBA, Summit, N.J.

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